top ten
in gastroenterologia
14^ EDIZIONE

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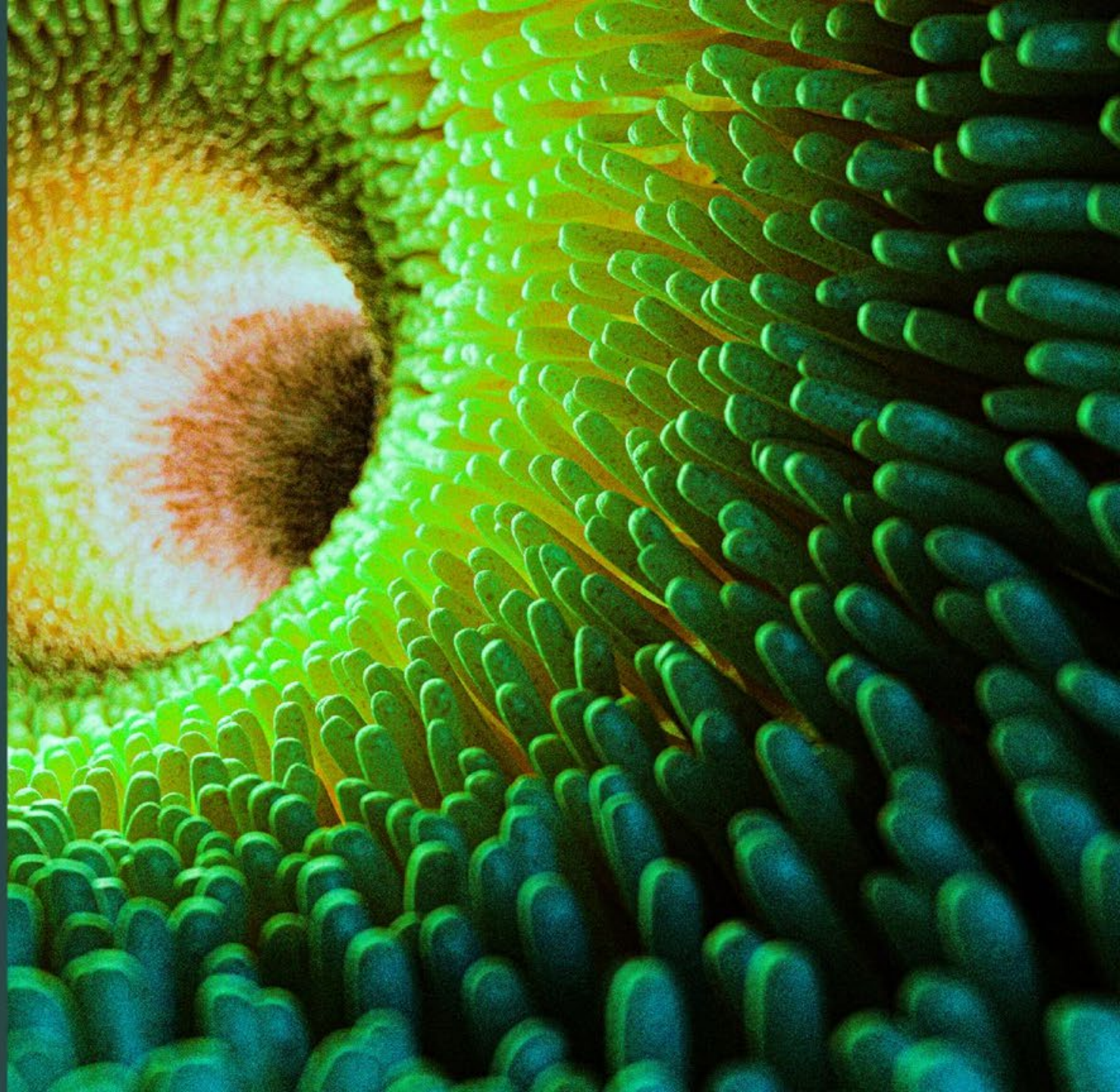

IBD: quale spazio terapeutico per il non-farmaco

Gianmichele Meucci

Ospedale San Giuseppe

Milano

Terapie "non farmacologiche"

- *Integratori*
- *Diete di esclusione*
- *Terapie "complementari"*

Terapie "non farmacologiche"

Integratori

- *Probiotici*
- *Curcumina*
- *Omega-3 fatty acids*

1

Probiotici nella terapia delle malattie infiammatorie intestinali

- *Formulazione De Simone*
- *Escherichia coli Nissle 1917*
- *Saccharomyces boulardii*
- *Lactobacillus (GG, acidophilus, rhamnosus, plantarum, reuteri)*
- *Bifidobacterium (longum, breve)*
- *Enterococcus spp*

Correction

Singh S, Feuerstein JD, Binion DG, et al. AGA Technical Review on the Management of Mild-to-Moderate Ulcerative Colitis. Gastroenterology 2019;156:769-808.e29

The studies in this review assessed a probiotic formulation previously known as VSL#3. The probiotic formulation that was assessed in these studies is now known by the generic name 'De Simone Formulation'. The current product known as VSL#3 is not the same formulation as the De Simone Formulation. The De Simone Formulation is available under the brand names Visbiome and Vivomixx.

Gastroenterology, September 2019

Until 2016, the De Simone Formulation (DSF) was sold as VSL#3® and had established its efficacy in inflammatory bowel diseases. ***After 2016, the VSL#3® product no longer contains DSF.*** *Accordingly, the VSL#3 references in the ECCO Guidelines 2017 exclusively endorse DSF supported by scientific evidence.*

ECCO Official Statement October 17th 2023

Review

Probiotics as a Coadjuvant Factor in Active or Quiescent Inflammatory Bowel Disease of Adults—A Meta-Analytical Study

Manuel Pabón-Carrasco [1], Lucia Ramirez-Baena [1,*], Samuel Vilar-Palomo [2], Aurora Castro-Méndez [3], Raúl Martos-García [1] and Isabel Rodríguez-Gallego [1]

Original Article

Efficacy and safety of probiotics in the induction and maintenance of inflammatory bowel disease remission: a systematic review and meta-analysis

Mingshi Chen[1], Yan Feng[2], Wanli Liu[1]

Probiotics in the Treatment of Inflammatory Bowel Diseases in Adulthood: A Systematic Review

Leonie Müller, Axel Lorentz

Review

The Role of Probiotics in Inducing and Maintaining Remission in Crohn's Disease and Ulcerative Colitis: A Systematic Review of the Literature

Georgios Vakadaris [1,†], Christos Stefanis [1,*,†], Elpida Giorgi [1], Merkourios Brouvalis [1], Chrysoula (Chrysa) Voidarou [2], Yiannis Kourkoutas [3], Christina Tsigalou [4] and Eugenia Bezirtzoglou [1]

Lead Article

Synbiotics improve clinical indicators of ulcerative colitis: systematic review with meta-analysis

Marcos Natal Rufino, Airan Lobo da Costa , Eloisa Nascimento Jorge, Viviane Ferreira Paiano, Marjori Leiva Camparoto, Rogéria Keller, and Hermann Bremer-Neto

Clinical effects and gut microbiota changes of using probiotics, prebiotics or synbiotics in inflammatory bowel disease: a systematic review and meta-analysis

Xiao-Feng Zhang[1] · Xiao-Xian Guan[1] · Yu-Jun Tang[1] · Jin-Feng Sun[1] · Xiao-Kai Wang[1] · Wei-Dong Wang[1] · Jian-Ming Fan[1]

Cochrane Library

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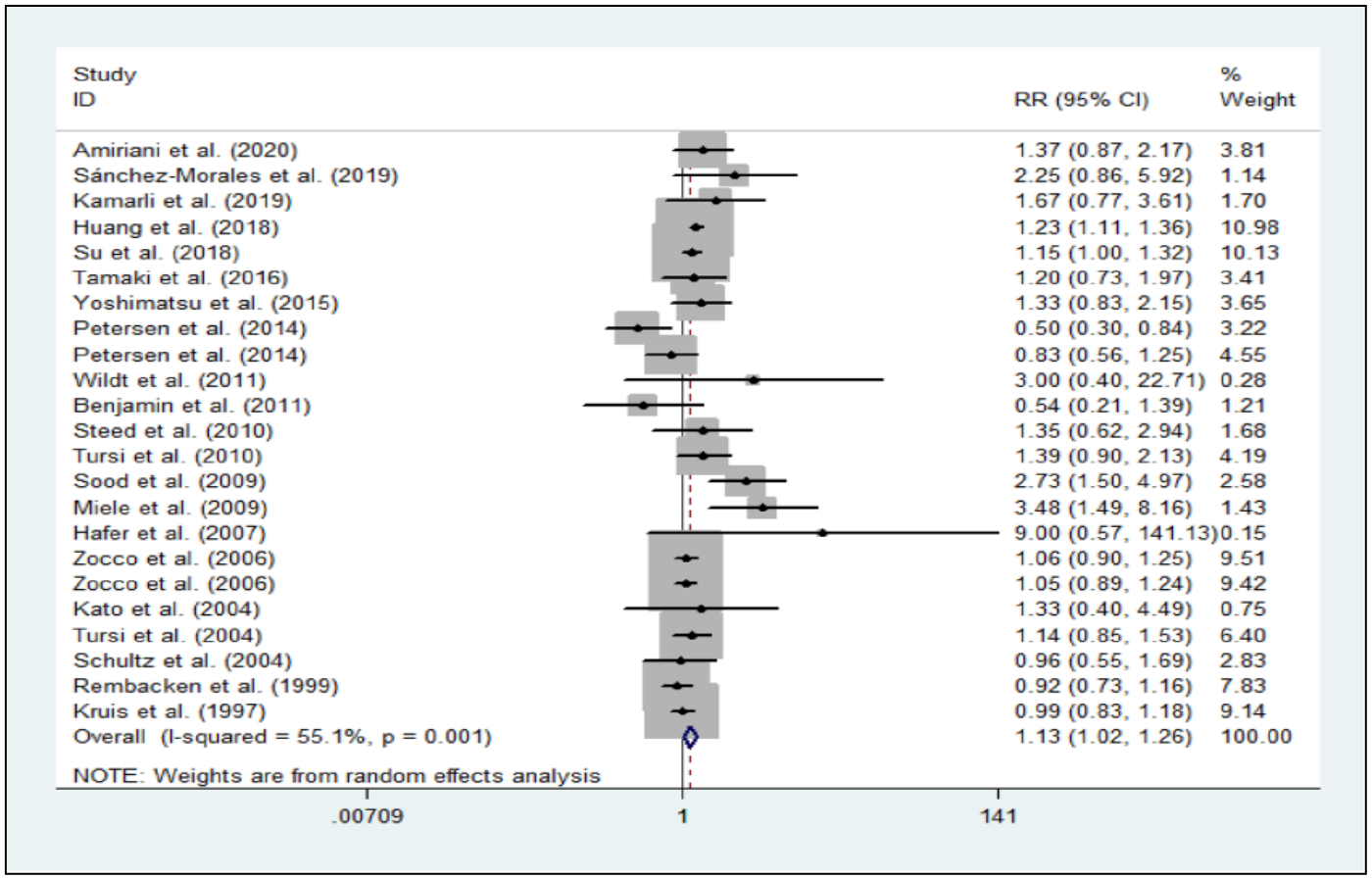
Probiotics for induction of remission in ulcerative colitis (Review)

Probiotics for maintenance of remission in ulcerative colitis (Review)

Probiotics for induction of remission in Crohn's disease (Review)

Clinical effects and gut microbiota changes of using probiotics, prebiotics or synbiotics in inflammatory bowel disease: a systematic review and meta-analysis



Zhang et al J Clin Nutr 2021

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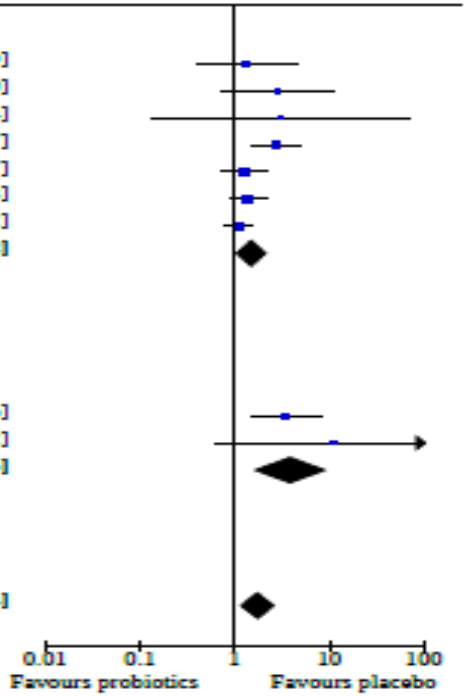
Probiotics for induction of remission in ulcerative colitis

Analysis 1.2. Comparison 1: Probiotics versus placebo, Outcome 2: Clinical remission: subgroup analysis by age

Study or Subgroup	Probiotic Events	Probiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Adult population						
Kato 2004	4	10	3	10	7.1%	1.33 [0.40 , 4.49]
Matthes 2010	20	70	2	20	6.0%	2.86 [0.73 , 11.20]
Sanchez-Morales 2019	1	17	0	17	1.4%	3.00 [0.13 , 68.84]
Sood 2009	33	77	11	70	15.6%	2.73 [1.50 , 4.97]
Tamaki 2016	15	28	12	28	16.7%	1.25 [0.72 , 2.17]
Tursi 2010	31	71	23	73	19.3%	1.39 [0.90 , 2.13]
Vejdani 2017	14	17	13	17	21.1%	1.08 [0.76 , 1.52]
Subtotal (95% CI)		**290**		**235**	**87.1%**	**1.49 [1.07 , 2.08]**
Total events:	118		64			
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 10.50$, df = 6 (P = 0.11); $I^2 = 43\%$						
Test for overall effect: Z = 2.33 (P = 0.02)						
1.2.2 Paediatric population						
Miele 2009	13	14	4	15	11.2%	3.48 [1.49 , 8.16]
Oliva 2011	5	20	0	20	1.7%	11.00 [0.65 , 186.62]
Subtotal (95% CI)		**34**		**35**	**12.9%**	**3.83 [1.69 , 8.66]**
Total events:	18		4			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.67$, df = 1 (P = 0.41); $I^2 = 0\%$						
Test for overall effect: Z = 3.23 (P = 0.001)						
Total (95% CI)		**324**		**270**	**100.0%**	**1.73 [1.19 , 2.54]**
Total events:	136		68			
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 17.89$, df = 8 (P = 0.02); $I^2 = 55\%$						
Test for overall effect: Z = 2.84 (P = 0.005)						
Test for subgroup differences: $Chi^2 = 4.42$, df = 1 (P = 0.04), $I^2 = 77.4\%$						



Kaur et al Cochrane Library 2020

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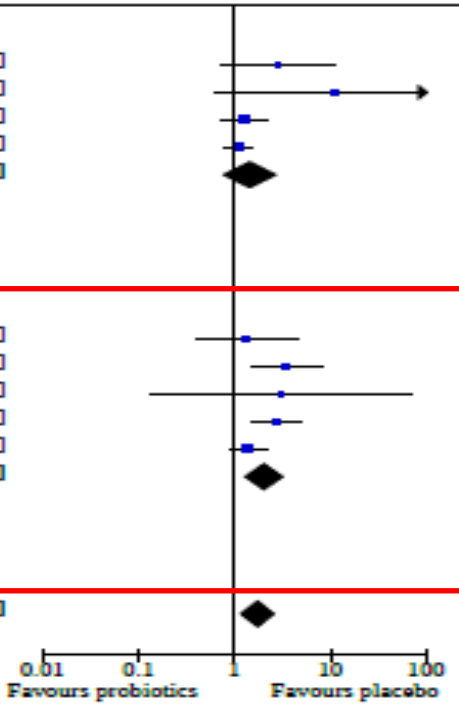
Probiotics for induction of remission in ulcerative colitis

Analysis 1.3. Comparison 1: Probiotics versus placebo, Outcome 3: Clinical remission: subgroup analysis by number of strains

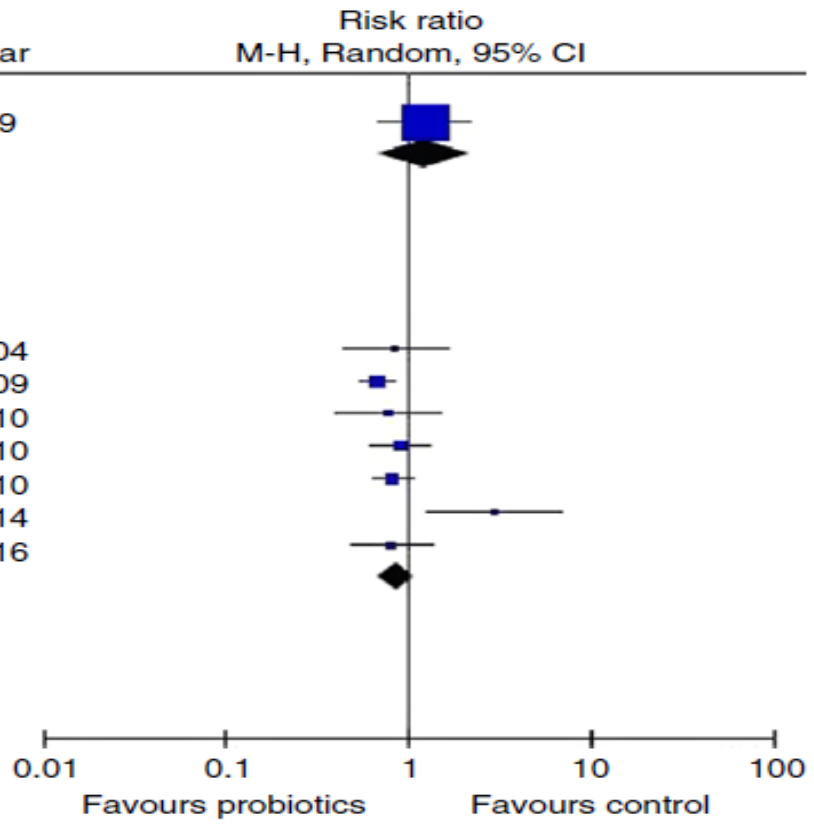
Study or Subgroup	Probiotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Single strain						
Matthes 2010	20	70	2	20	6.0%	2.86 [0.73 , 11.20]
Oliva 2011	5	20	0	20	1.7%	11.00 [0.65 , 186.62]
Tamaki 2016	15	28	12	28	16.7%	1.25 [0.72 , 2.17]
Vejdani 2017	14	17	13	17	21.1%	1.08 [0.76 , 1.52]
Subtotal (95% CI)		**135**		**85**	**45.4%**	**1.44 [0.79 , 2.63]**
Total events:	54		27			
Heterogeneity: Tau² = 0.18; Chi² = 7.00, df = 3 (P = 0.07); I² = 57%						
Test for overall effect: Z = 1.18 (P = 0.24)						
1.3.2 Multiple strains						
Kato 2004	4	10	3	10	7.1%	1.33 [0.40 , 4.49]
Miele 2009	13	14	4	15	11.2%	3.48 [1.49 , 8.16]
Sanchez-Morales 2019	1	17	0	17	1.4%	3.00 [0.13 , 68.84]
Sood 2009	33	77	11	70	15.6%	2.73 [1.50 , 4.97]
Tursi 2010	31	71	23	73	19.3%	1.39 [0.90 , 2.13]
Subtotal (95% CI)		**189**		**185**	**54.6%**	**2.02 [1.31 , 3.12]**
Total events:	82		41			
Heterogeneity: Tau² = 0.08; Chi² = 5.89, df = 4 (P = 0.21); I² = 32%						
Test for overall effect: Z = 3.18 (P = 0.001)						
Total (95% CI)		**324**		**270**	**100.0%**	**1.73 [1.19 , 2.54]**
Total events:	136		68			
Heterogeneity: Tau² = 0.15; Chi² = 17.89, df = 8 (P = 0.02); I² = 55%						
Test for overall effect: Z = 2.84 (P = 0.005)						
Test for subgroup differences: Chi² = 0.80, df = 1 (P = 0.37), I² = 0%						



Kaur et al Cochrane Library 2020

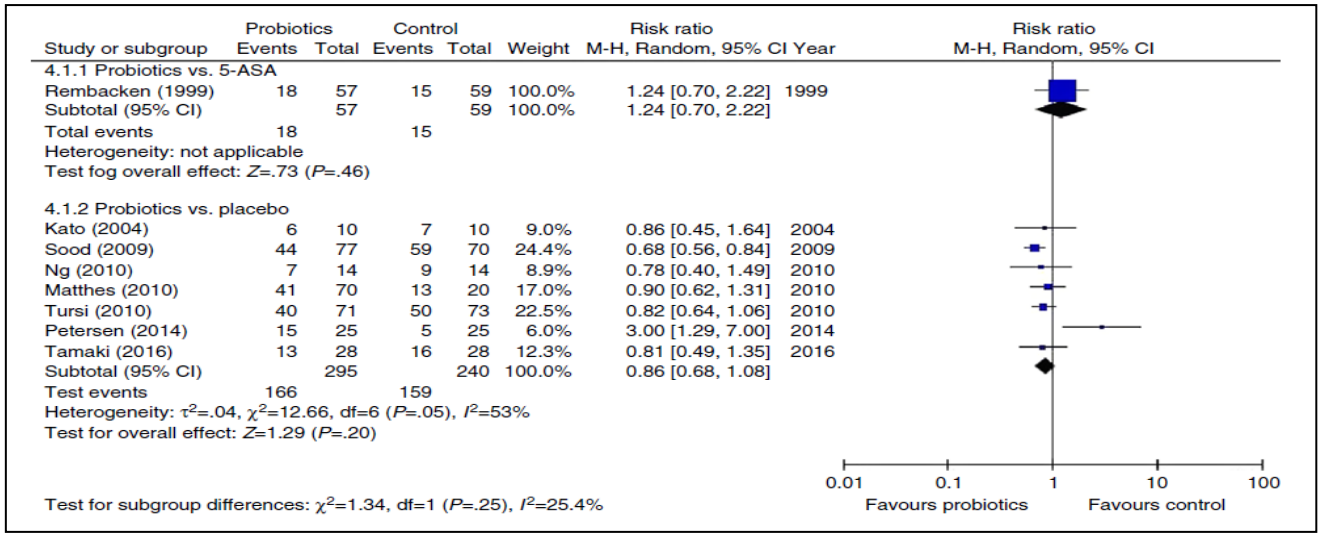
2 Probiotics for induction of remission in ulcerative colitis

Study or subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
4.1.1 Probiotics vs. 5-ASA							
Rembacken (1999)	18	57	15	59	100.0%	1.24 [0.70, 2.22]	1999
Subtotal (95% CI)		57		59	100.0%	1.24 [0.70, 2.22]	
Total events	18		15				
Heterogeneity: not applicable							
Test fog overall effect: Z=.73 (P=.46)							
4.1.2 Probiotics vs. placebo							
Kato (2004)	6	10	7	10	9.0%	0.86 [0.45, 1.64]	2004
Sood (2009)	44	77	59	70	24.4%	0.68 [0.56, 0.84]	2009
Ng (2010)	7	14	9	14	8.9%	0.78 [0.40, 1.49]	2010
Matthes (2010)	41	70	13	20	17.0%	0.90 [0.62, 1.31]	2010
Tursi (2010)	40	71	50	73	22.5%	0.82 [0.64, 1.06]	2010
Petersen (2014)	15	25	5	25	6.0%	3.00 [1.29, 7.00]	2014
Tamaki (2016)	13	28	16	28	12.3%	0.81 [0.49, 1.35]	2016
Subtotal (95% CI)		295		240	100.0%	0.86 [0.68, 1.08]	
Test events	166		159				
Heterogeneity: τ^2=.04, χ^2=12.66, df=6 (P=.05), I^2=53%							
Test for overall effect: Z=1.29 (P=.20)							
Test for subgroup differences: χ^2=1.34, df=1 (P=.25), I^2=25.4%							

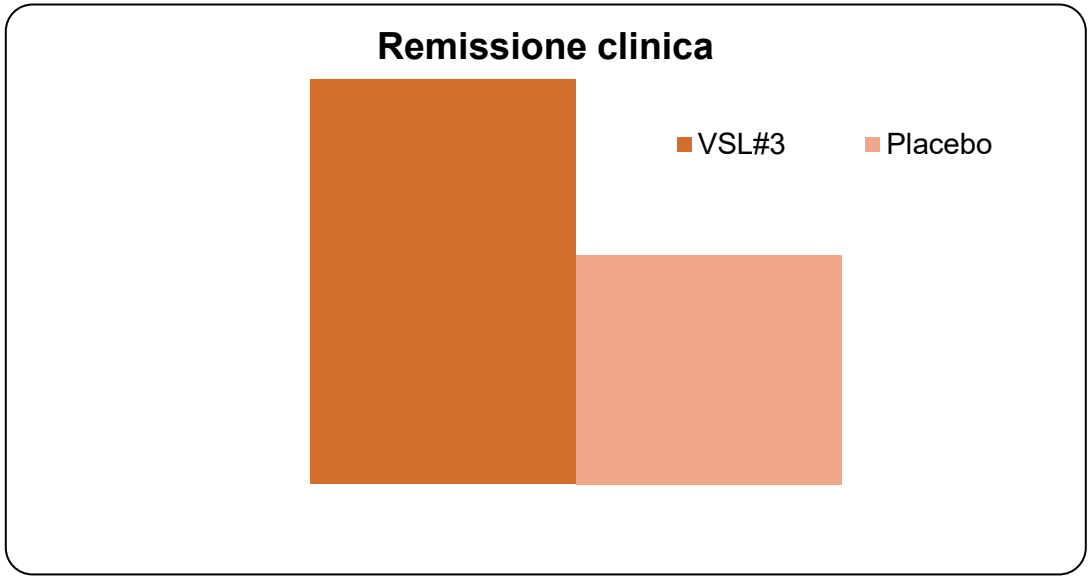


Dewa et al APT 2017

Probiotics for induction of remission in ulcerative colitis



Study or subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
4.1.1 Probiotics vs. 5-ASA							
Rembacken (1999)	18	57	15	59	100.0%	1.24 [0.70, 2.22]	1999
Subtotal (95% CI)		57		59	100.0%	1.24 [0.70, 2.22]	
Total events	18		15				
Heterogeneity: not applicable							
Test fog overall effect: Z=.73 (P=.46)							
4.1.2 Probiotics vs. placebo							
Kato (2004)	6	10	7	10	9.0%	0.86 [0.45, 1.64]	2004
Sood (2009)	44	77	59	70	24.4%	0.68 [0.56, 0.84]	2009
Ng (2010)	7	14	9	14	8.9%	0.78 [0.40, 1.49]	2010
Matthes (2010)	41	70	13	20	17.0%	0.90 [0.62, 1.31]	2010
Tursi (2010)	40	71	50	73	22.5%	0.82 [0.64, 1.06]	2010
Petersen (2014)	15	25	5	25	6.0%	3.00 [1.29, 7.00]	2014
Tamaki (2016)	13	28	16	28	12.3%	0.81 [0.49, 1.35]	2016
Subtotal (95% CI)		295		240	100.0%	0.86 [0.68, 1.08]	
Test events	166		159				
Heterogeneity: τ^2=.04, χ^2=12.66, df=6 (P=.05), I^2=53%							
Test for overall effect: Z=1.29 (P=.20)							
Test for subgroup differences: χ^2=1.34, df=1 (P=.25), I^2=25.4%							



Dewa et al APT 2017

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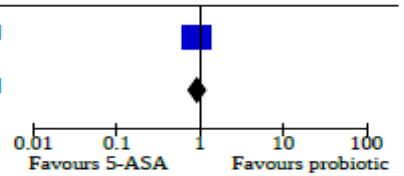
Probiotics for induction of remission in ulcerative colitis

Analysis 2.1. Comparison 2: Probiotics versus 5-aminosalicylic acid (5-ASA) (mesalazine), Outcome 1: Clinical remission

Study or Subgroup	Probiotic Events	Probiotic Total	5-ASA Events	5-ASA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rembacken 1999	39	57	44	59	100.0%	0.92 [0.73 , 1.16]
Total (95% CI)		**57**		**59**	**100.0%**	**0.92 [0.73 , 1.16]**
Total events:	39		44			

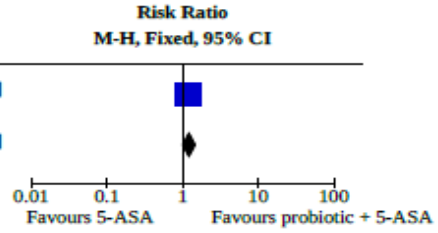
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3: Probiotics plus 5-aminosalicylic acid (5-ASA) (mesalazine) versus 5-ASA (mesalazine), Outcome 1: Remission (based on Sunderland disease activity index)

Study or Subgroup	Probiotic + 5-ASA Events	Probiotic + 5-ASA Total	5-ASA Events	5-ASA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Liu 2014	39	42	32	42	100.0%	1.22 [1.01 , 1.47]
Total (95% CI)		**42**		**42**	**100.0%**	**1.22 [1.01 , 1.47]**
Total events:	39		32			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.05 (P = 0.04)
Test for subgroup differences: Not applicable



Kaur et al Cochrane Library 2020

Probiotic Mix VSL#3 Is Effective Adjunctive Therapy for Mild to Moderately Active Ulcerative Colitis: A Meta-analysis

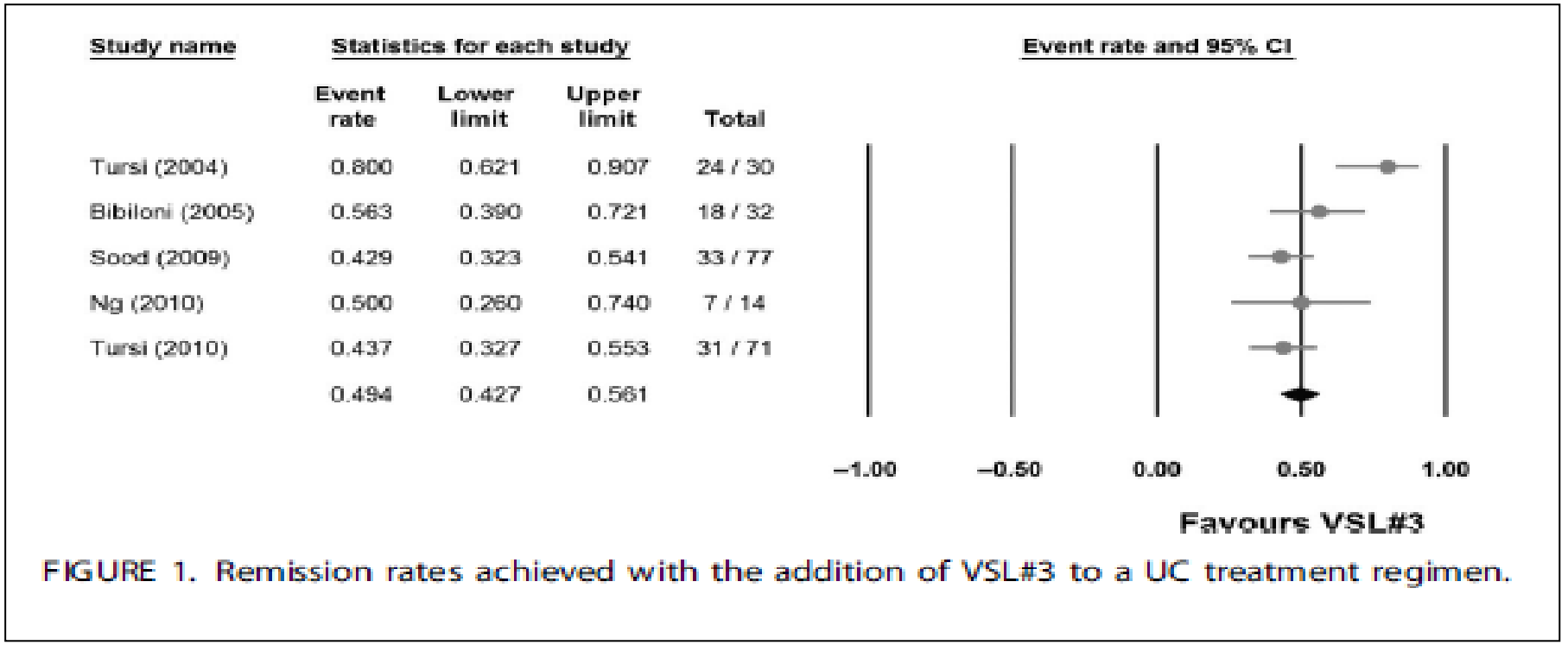


FIGURE 1. Remission rates achieved with the addition of VSL#3 to a UC treatment regimen.

***UC treatment regimen*: grande eterogeneità fra gli studi valutati**

Mardini et al IBD 2014

3

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Probiotics for induction of remission in ulcerative colitis

Low-certainty evidence *suggests that probiotics* ***may induce clinical remission in active ulcerative colitis when compared to placebo.***

There may be little or no difference in clinical remission with probiotics alone compared to 5-ASA.

There is limited evidence from a single study *which failed to provide a definition of remission, that probiotics* ***may slightly improve the induction of remission when used in combination with 5-ASA.***

There was no evidence to assess whether probiotics are effective in people with severe and more extensive disease, or if specific preparations are superior to others.

Further targeted and appropriately designed RCTs are needed to address the gaps in the evidence base*. In particular, appropriate powering of studies and the use of standardised participant groups and outcome measures in line with the wider field are needed, as well as reporting to minimise risk of bias.*

Kaur et al Cochrane Library 2020

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Cochrane Database of Systematic Reviews

Probiotics for maintenance of remission in ulcerative colitis

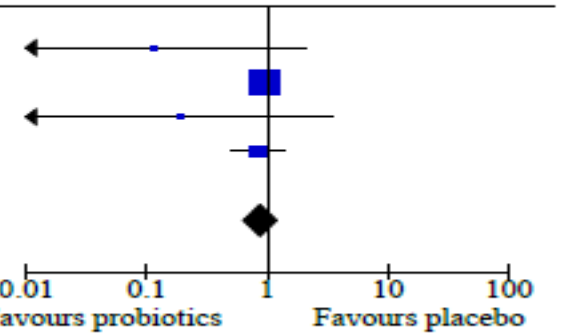
Analysis 1.1. Comparison 1: Probiotics versus placebo, Outcome 1: Clinical relapse

Study or Subgroup	Probiotics Events	Probiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bjarnason 2019	0	40	4	41	1.2%	0.11 [0.01 , 2.05]
Matsuoka 2018	55	98	58	97	68.2%	0.94 [0.74 , 1.19]
NCT02361957	0	13	2	12	1.1%	0.19 [0.01 , 3.52]
Yasushi 2015	14	30	17	30	29.5%	0.82 [0.50 , 1.35]
Total (95% CI)		**181**		**180**	**100.0%**	**0.87 [0.63 , 1.18]**
Total events:	69		81			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.60$, $df = 3$ ($P = 0.31$); $I^2 = 17\%$

Test for overall effect: $Z = 0.91$ ($P = 0.36$)

Test for subgroup differences: Not applicable



Iheozor-Ejiofor et al Cochrane Library 2020

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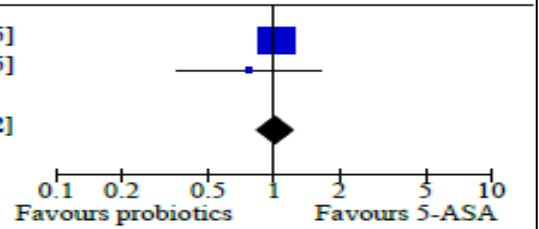
Probiotics for maintenance of remission in ulcerative colitis

Analysis 2.1. Comparison 2: Probiotics versus 5-aminosalicylic acid (5-ASA) (mesalazine), Outcome 1: Clinical relapse

Study or Subgroup	Probiotics Events	Probiotics Total	5-ASA Events	5-ASA Total	Weight	Risk Ratio M-H, Random, 95% CI
Kruis 2004	92	162	91	165	94.0%	1.03 [0.85 , 1.25]
Zocco 2006	10	65	12	60	6.0%	0.77 [0.36 , 1.65]
Total (95% CI)		**227**		**225**	**100.0%**	**1.01 [0.84 , 1.22]**
Total events:	102		103			

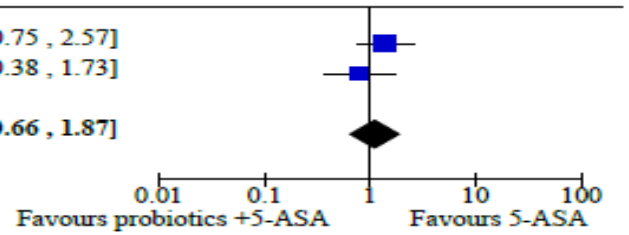
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3: Probiotic + 5-aminosalicylic acid (5-ASA) (mesalazine) versus 5-ASA (mesalazine), Outcome 1: Clinical relapse

Study or Subgroup	Probiotic + 5-ASA Events	Probiotic + 5-ASA Total	5-ASA Events	5-ASA Total	Weight	Risk Ratio M-H, Random, 95% CI
Kruis 1997 (1)	18	60	13	60	58.8%	1.38 [0.75 , 2.57]
Zocco 2006	10	62	12	60	41.2%	0.81 [0.38 , 1.73]
Total (95% CI)		**122**		**120**	**100.0%**	**1.11 [0.66 , 1.87]**
Total events:	28		25			

Heterogeneity: Tau² = 0.02; Chi² = 1.17, df = 1 (P = 0.28); I² = 15%
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable



Iheozor-Ejiofor et al Cochrane Library 2020

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Probiotics for maintenance of remission in ulcerative colitis

***The effectiveness of probiotics for the maintenance of remission in ulcerative colitis remains unclear**.*
***This is due to low- to very low certainty evidence from poorly conducted studies**, which contribute limited amounts of data from a small number of participants.*
***Future trials comparing probiotics with 5-ASA rather than placebo will better reflect conventional care** given to people with ulcerative colitis.*
Appropriately powered studies with a minimum length of 12 months are needed

Iheozor-Ejiofor et al Cochrane Library 2020

4 Escherichia coli Nissle 1917 vs mesalazina nella colite ulcerosa in remissione: metaanalisi

Study or Subgroup	EcN Events	EcN Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Henker 2008	8	24	3	10	6.8%	1.17 [0.24, 5.76]
Kruis 1997	8	50	6	53	11.7%	1.49 [0.48, 4.65]
Kruis 2004	40	110	38	112	57.5%	1.11 [0.64, 1.93]
Rembacken 1999	26	39	32	44	24.0%	0.75 [0.29, 1.92]
Total (95% CI)		**223**		**219**	**100.0%**	**1.07 [0.70, 1.64]**
Total events	82		79			

Heterogeneity: Chi² = 0.91, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

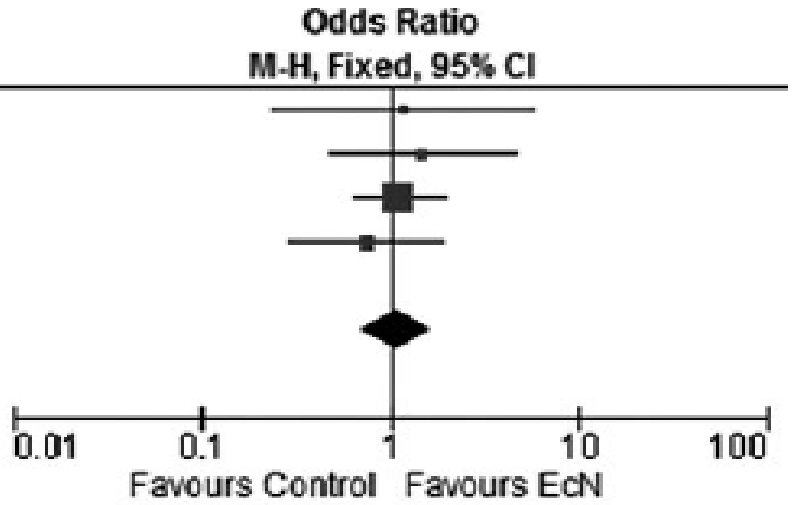


Fig. 3. Forest plot of the efficacy of EcN in maintaining remission for ulcerative colitis.

Losurdo et al J Gastrointestin Liver Dis 2015

Prophylaxis of Pouchitis Onset With Probiotic Therapy: A Double-Blind, Placebo-Controlled Trial

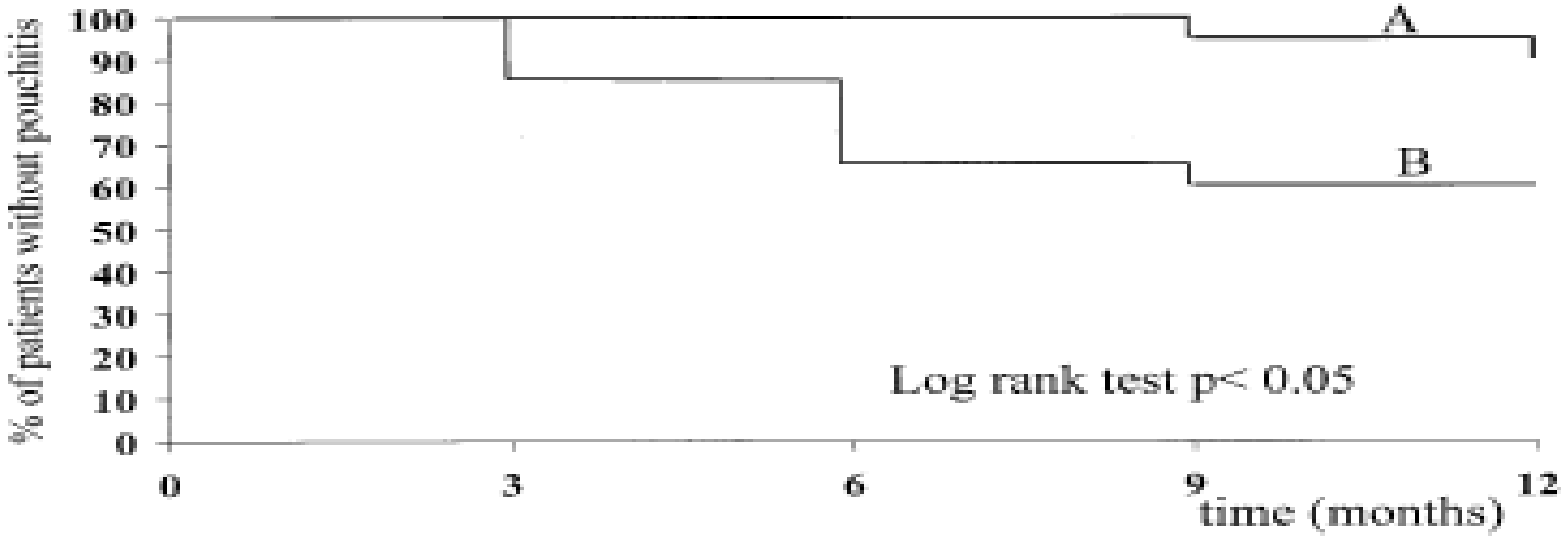
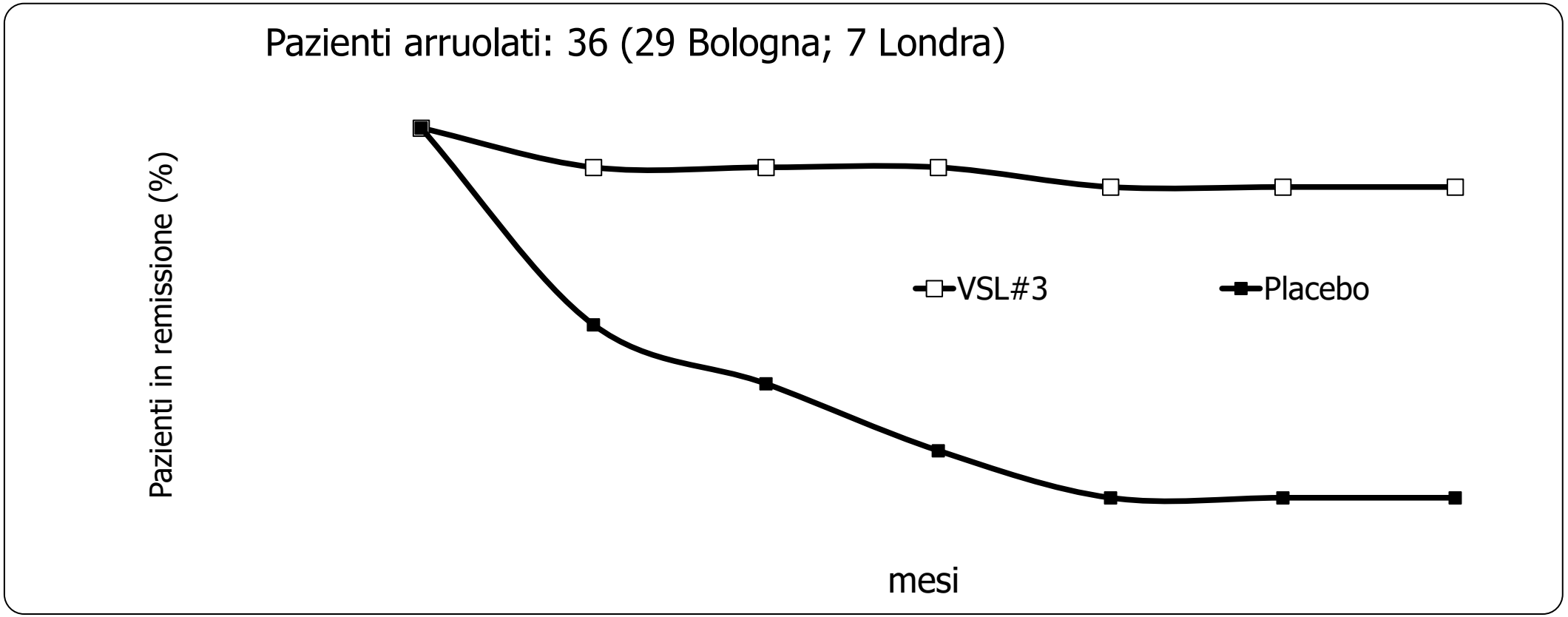


Figure 2. Kaplan–Meier estimates of cumulative rates of pouchitis during treatment with (*A*) VSL#3 or (*B*) placebo.

Gionchetti et al Gastroenterology 2003

VSL#3 nella terapia di mantenimento della pouchite ricorrente (dopo remissione indotta da antibiotici)



Mimura et al Gut 2004

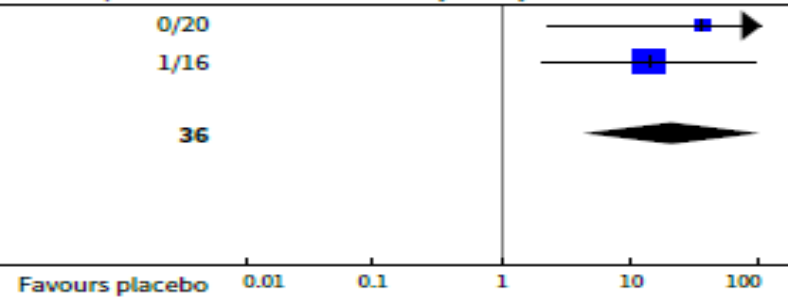
Cochrane Library

Cochrane Database of Systematic Reviews

VSL#3 nella terapia di mantenimento della pouchite ricorrente (dopo remissione indotta da antibiotici)

Analysis 7.1. Comparison 7 VLS#3 versus placebo, Outcome 1 Maintenance of clinical remission.

Study or subgroup	VSL#3 n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gionchetti 2000	17/20	0/20		31.03%	35[2.25,544.92]
Mimura 2004	17/20	1/16		68.97%	13.6[2.02,91.53]
Total (95% CI)	**40**	**36**		**100%**	**20.24[4.28,95.81]**
Total events: 34 (VSL#3), 1 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.32, df=1(P=0.57); I²=0%					
Test for overall effect: Z=3.79(P=0)					



Singh et al Cochrane Library 2015

Cochrane Library

Cochrane Database of Systematic Reviews

Treatment and prevention of pouchitis aer ileal pouch-anal anastomosis for chronic ulcerative colitis

*For chronic pouchitis, **low quality evidence** suggests that VSL#3 may be more effective than placebo for maintenance of remission.*

*For the prevention of pouchitis, **low quality evidence** suggests that VSL#3 may be more eLective than placebo.*

***Well designed, adequately powered studies are needed** to determine the optimal therapy for the treatment and prevention of pouchitis*

Singh et al Cochrane Library 2015

Treatment of pouchitis, Crohn's disease, cuffitis, and other inflammatory disorders of the pouch: consensus guidelines from the International Ileal Pouch Consortium

Shen et al Lancet Gastroenterolo Hepatol 2022

		Evidence level (range 1–5)*	Grade of recommendation (range A–D)†
1. Pouchitis			
1. Primary prophylaxis of the first episodes of pouchitis after stoma closure			
1.1a	Routine primary prophylaxis for the initial episodes of pouchitis with antibiotics is not recommended.	4	C
1.1b	Primary prophylaxis for the initial episodes of pouchitis with certain probiotics might be beneficial in patients at risk of pouchitis.	2b	C
2. Therapy for acute pouchitis			
1.2a	First episodes of acute pouchitis can be treated with ciprofloxacin or metronidazole.	2b	B
1.2b	Routine use of probiotics for the treatment of pouchitis is not recommended due to the lack of evidence.	4	C
1.2c	Topical budesonide can be used as a second-line therapy for the treatment of acute pouchitis for those who do not respond to antibiotic therapy.	4	D
3. Induction therapy for chronic pouchitis			
1.3a	A prolonged course (eg, 4 weeks) of combined antibiotic therapy (ciprofloxacin combined with metronidazole, tinidazole, or rifaximin) can be used for the treatment of pouchitis refractory to single antibiotics.‡ However, maintenance of antibiotic-induced remission might require non-antibiotic agents, such as biologics.	4	C
1.3b	Oral or topical budesonide can be used for chronic antibiotic-refractory pouchitis, especially in patients with comorbid primary sclerosing cholangitis.	4	C
1.3c	The anti-integrin agent vedolizumab is preferred over anti-TNF agents for the induction therapy of chronic antibiotic-refractory pouchitis.	1a	A
1.3d	Anti-TNF agents (eg, infliximab and adalimumab) can be used for induction therapy in chronic antibiotic-refractory pouchitis.	4	C
1.3e	The anti-IL-12/23 agent ustekinumab can be used for induction therapy in chronic antibiotic-refractory pouchitis.	4	C
1.3f	Failure of a specific agent (eg, a biologic) before colectomy does not preclude the use of the same agent for the treatment of chronic inflammatory pouch disorders (such as pouchitis).	4	C
4. Maintenance therapy (secondary prophylaxis) for chronic antibiotic-dependent pouchitis			
1.4a	Following induction therapy with antibiotics, some patients can develop chronic antibiotic-dependent pouchitis, requiring long-term maintenance therapy.	2c	B
1.4b	Certain probiotics can be used as maintenance therapy for secondary prophylaxis in patients with relapsing pouchitis after remission induced by antibiotics.	2b	C
1.4c	Antibiotics can be used as maintenance therapy for secondary prophylaxis of chronic antibiotic-dependent pouchitis.	4	D
5. Maintenance therapy for chronic antibiotic-refractory pouchitis			

Cochrane Library

Cochrane Database of Systematic Reviews

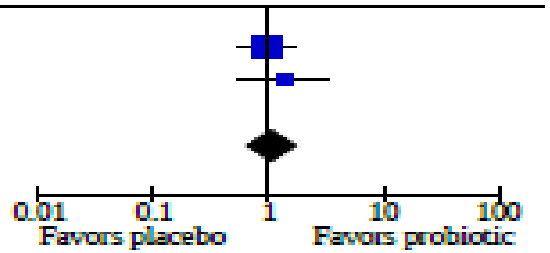
Probiotics for induction of remission in Crohn's disease

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Schultz 2004	4	5	5	6	71.6%	0.96 [0.55 , 1.69]
Steed 2010	8	19	5	16	28.4%	1.35 [0.55 , 3.31]
Total (95% CI)		**24**		**22**	**100.0%**	**1.06 [0.65 , 1.71]**
Total events:	12		10			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.57$, df = 1 (P = 0.45); $I^2 = 0\%$

Test for overall effect: Z = 0.23 (P = 0.82)

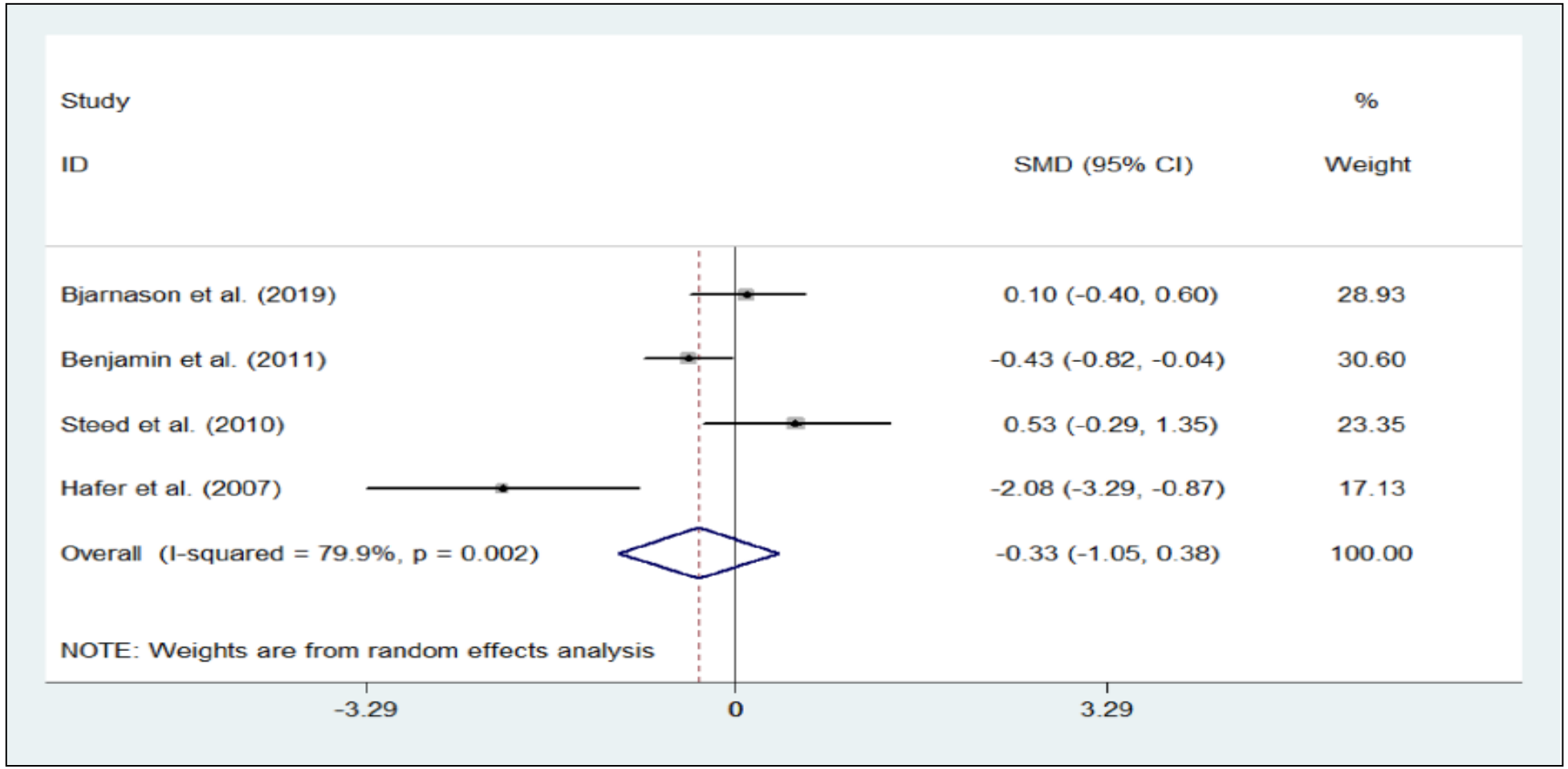
Test for subgroup differences: Not applicable



***The available evidence is very uncertain about the efficacy or safety of probiotics**, when compared with placebo, for induction of remission in Crohn's disease. **There is a lack of well-designed RCTs** in this area and further research is needed.*

Limketkai et al Cochrane Library 2020

Probiotics for induction of remission in Crohn's disease



Zhang et al J Clin Nutr 2021

Probiotici per la prevenzione della recidiva post-chirurgica

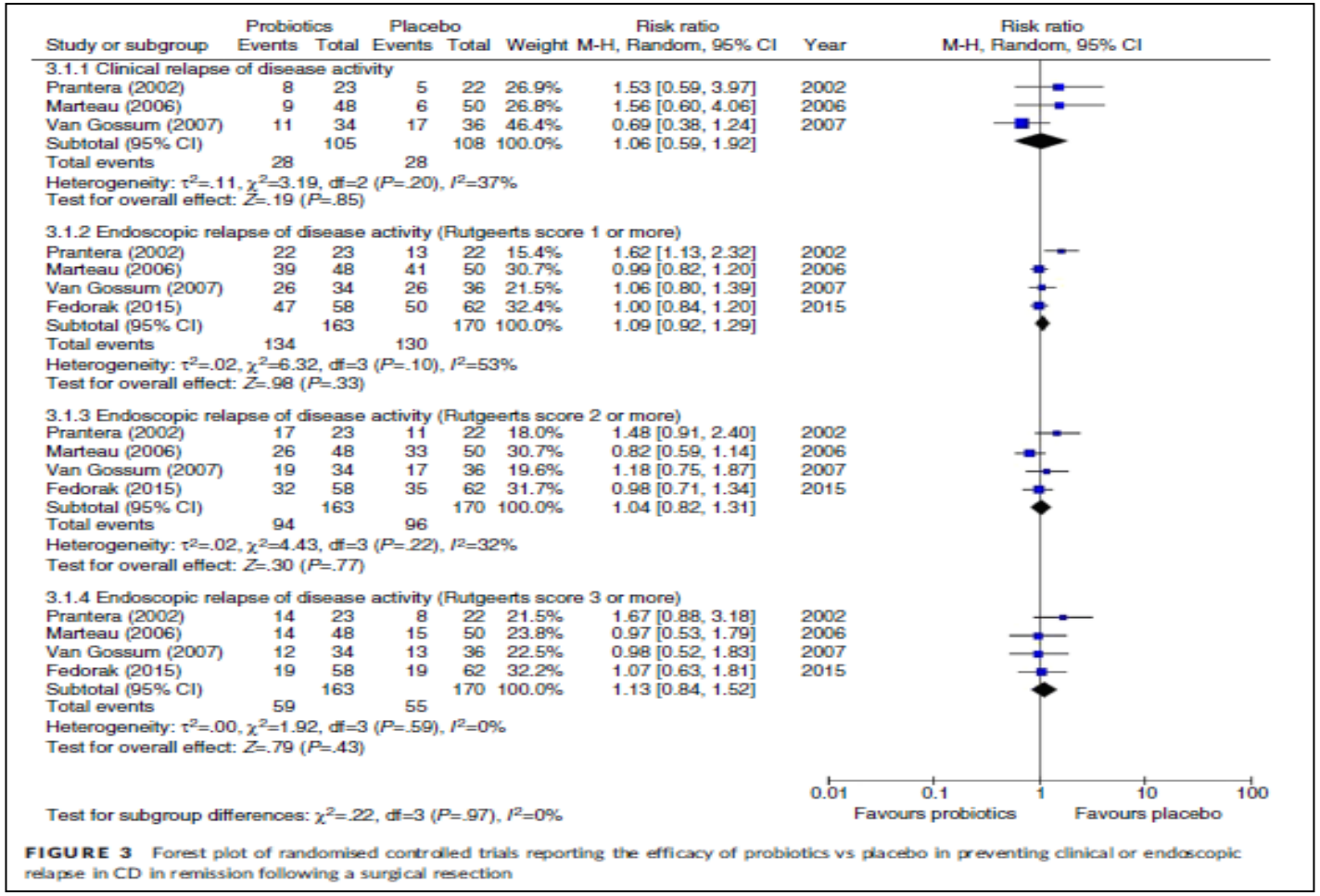


FIGURE 3 Forest plot of randomised controlled trials reporting the efficacy of probiotics vs placebo in preventing clinical or endoscopic relapse in CD in remission following a surgical resection

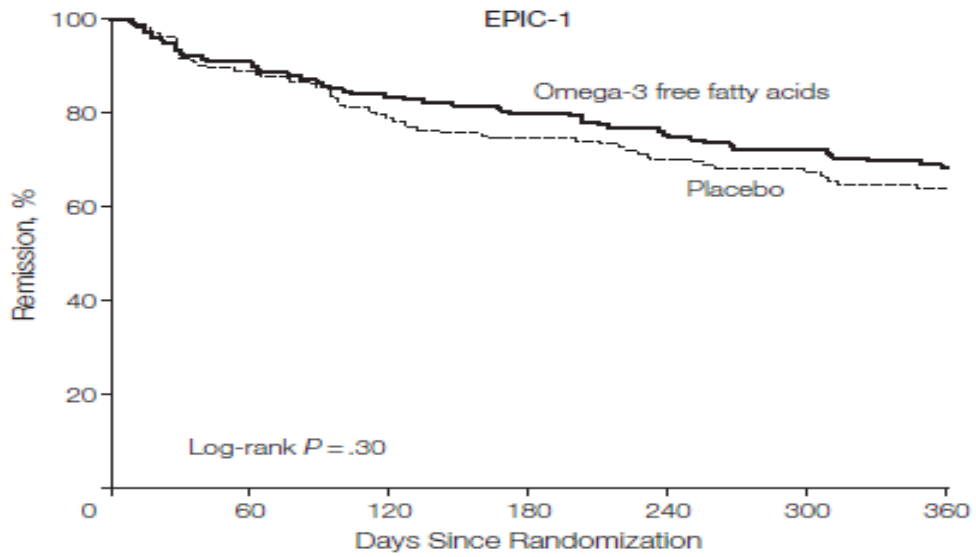
Derwa et al et al APT 2017

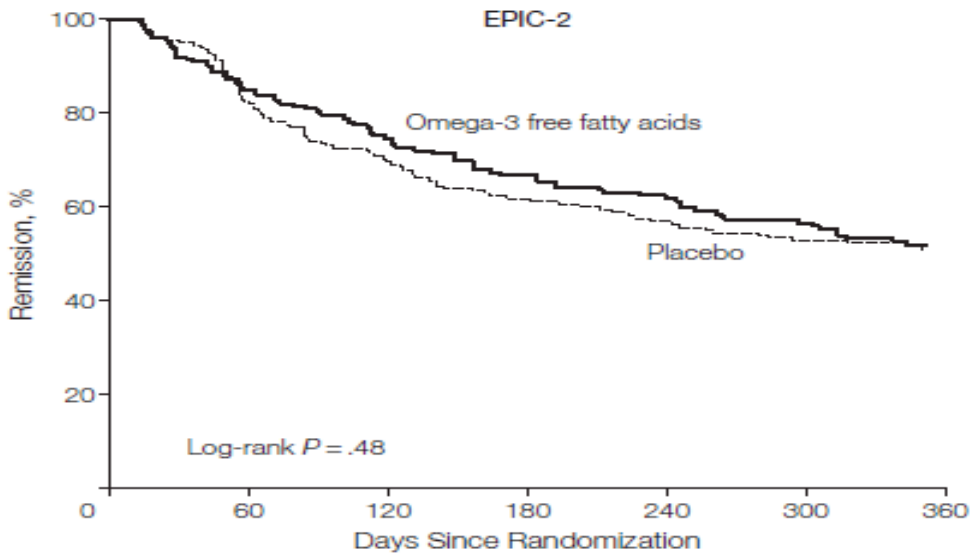
Probiotici nella terapia della colite ulcerosa
Possibili indicazioni

- *Formulazione de Simone nella terapia di mantenimento della pouchite antibiotico-dipendente*
- *Escherichia Coli Nissle 1917 nella terapia di mantenimento della colite ulcerosa* ***in pazienti intolleranti a mesalazina***
- *Probiotici contenenti ceppi multipli* ***in aggiunta a mesalazina*** *nella terapia di mantenimento della colite ulcerosa*

Omega-3 Free Fatty Acids for the Maintenance of Remission in Crohn's Disease The EPIC Randomized Controlled Trials

Figure 2. Kaplan-Meier Estimates of the Time to Relapse in the Omega-3 Free Fatty Acids and Placebo Groups for EPIC-1 and EPIC-2





No. at risk							
Omega-3 free fatty acids	183	157	140	132	118	113	83
Placebo	180	152	130	120	107	102	77

Omega-3 free fatty acids	187	150	126	110	95	87	78
Placebo	188	149	124	106	96	87	83

EPIC indicates Epanova Program in Crohn's Study.

Feagan et al, JAMA 2008

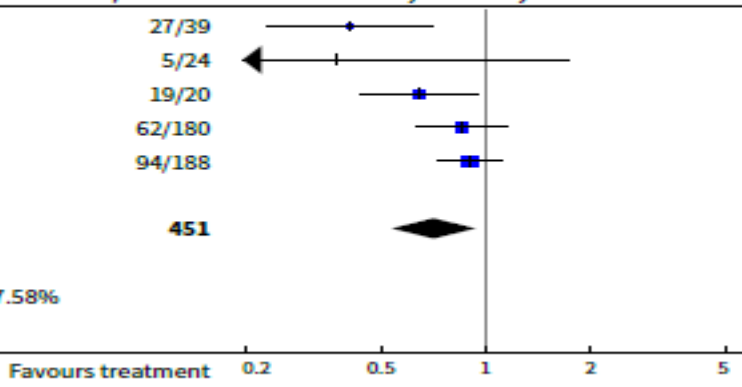
Cochrane Library

Cochrane Database of Systematic Reviews

Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease (Review)

Analysis 1.2. Comparison 1 Omega-3 versus placebo, Outcome 2 Relapse rate at one year (enteric coated studies).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Belluzzi 1996	11/39	27/39		15.61%	0.41[0.24,0.7]
Belluzzi 1997	2/26	5/24		2.95%	0.37[0.08,1.73]
Romano 2005	11/18	19/20		22.5%	0.64[0.44,0.94]
Feagan 2008a	54/183	62/180		26.91%	0.86[0.63,1.16]
Feagan 2008b	84/187	94/188		32.04%	0.9[0.73,1.11]
Total (95% CI)	**453**	**451**		**100%**	**0.71[0.54,0.93]**
Total events: 162 (Treatment), 207 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=9.43, df=4(P=0.05); I^2=57.58%					
Test for overall effect: Z=2.45(P=0.01)					



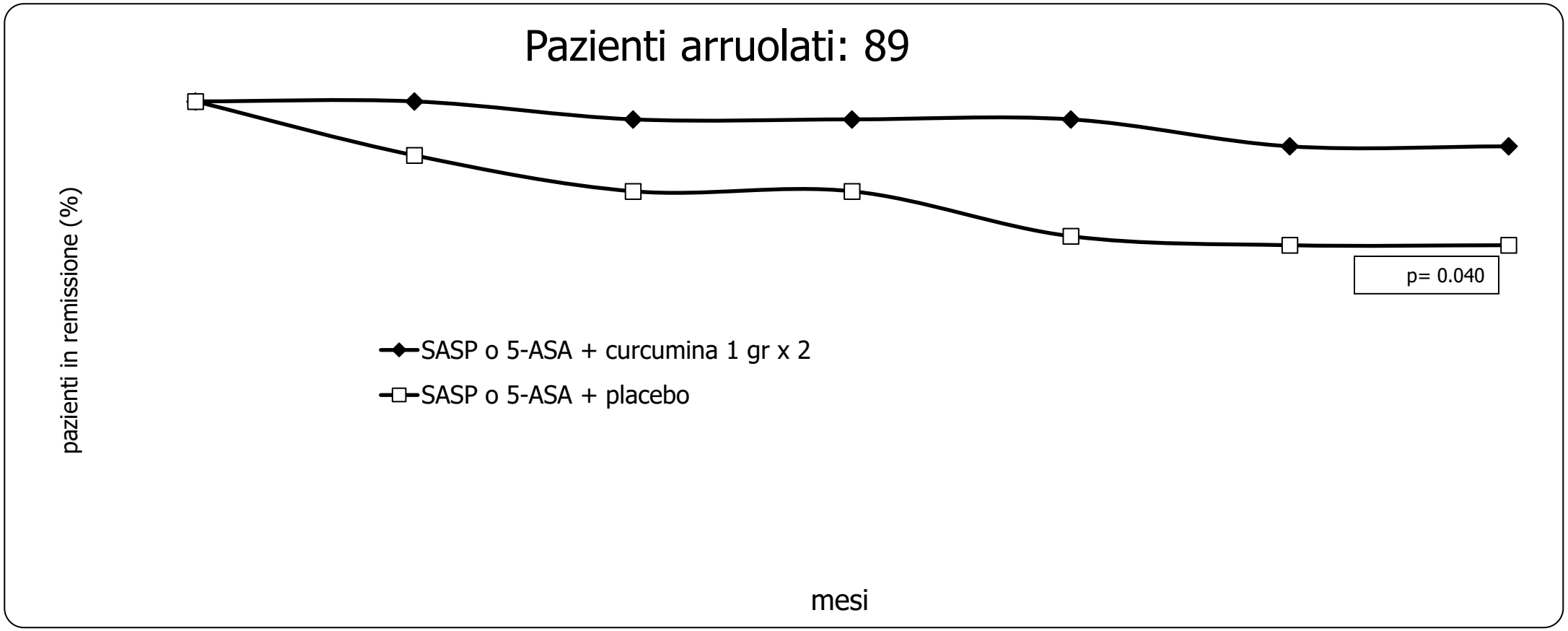
Authors' conclusions

Evidence from two large high quality studies suggests that omega 3 fatty acids are probably ineffective for maintenance of remission in CD.

Omega 3 fatty acids appear to be safe although they may cause diarrhea and upper gastrointestinal tract symptoms.

Lev-Tzion R, et al Cochrane Library 2014

Curcumin Maintenance Therapy for Ulcerative Colitis: Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial



Hanai et al, Clin Gastroenterol Hepatol 2006

Curcumin in Combination With Mesalamine Induces Remission in Patients With Mild-to-Moderate Ulcerative Colitis in a Randomized Controlled Trial

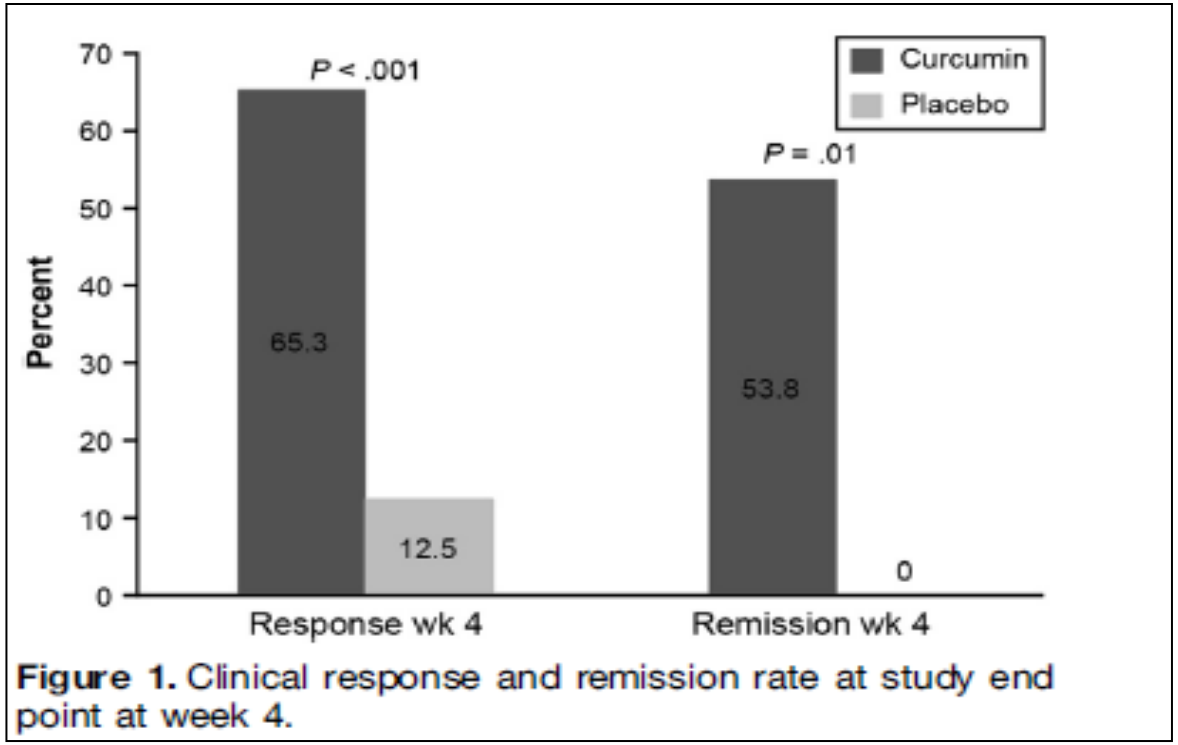
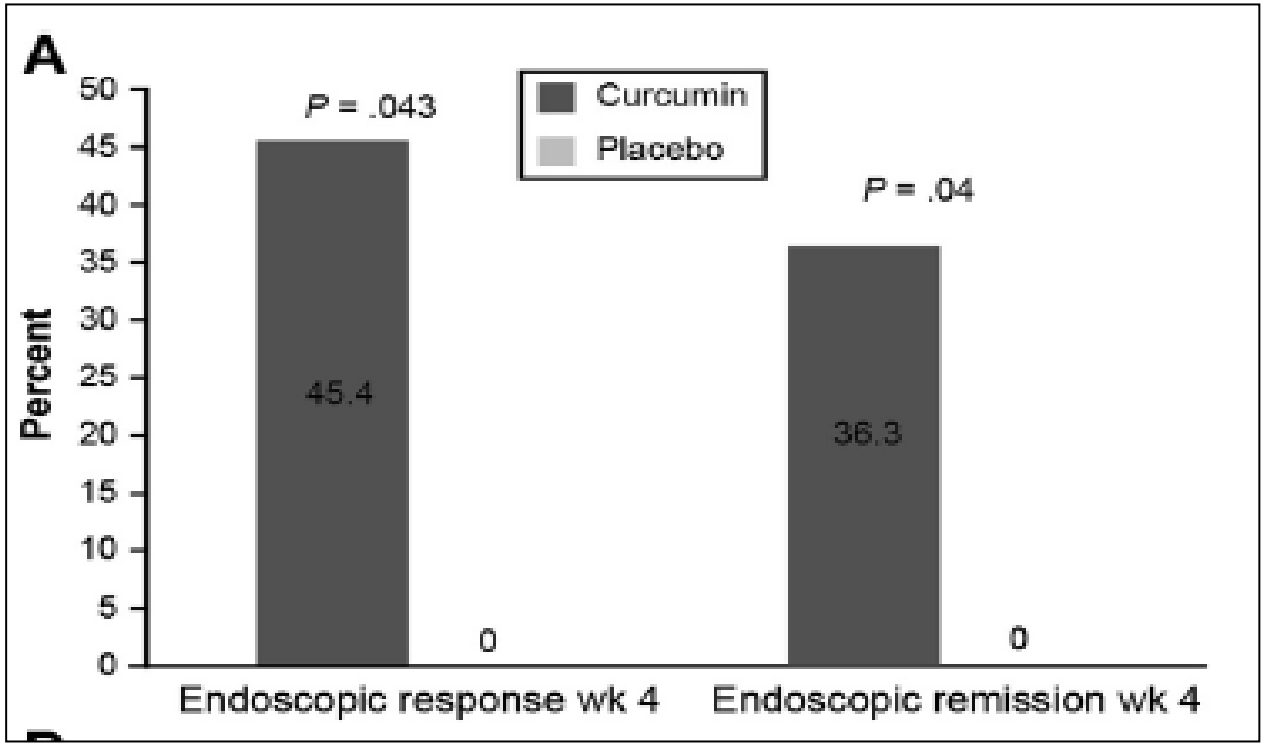


Figure 1. Clinical response and remission rate at study end point at week 4.



Curcumina 3 gr/die

Lang et al, Clin Gastroenterology Hepatol 2015

Novel Bioenhanced Curcumin With Mesalamine for Induction of Clinical and Endoscopic Remission in Mild-to-Moderate Ulcerative Colitis

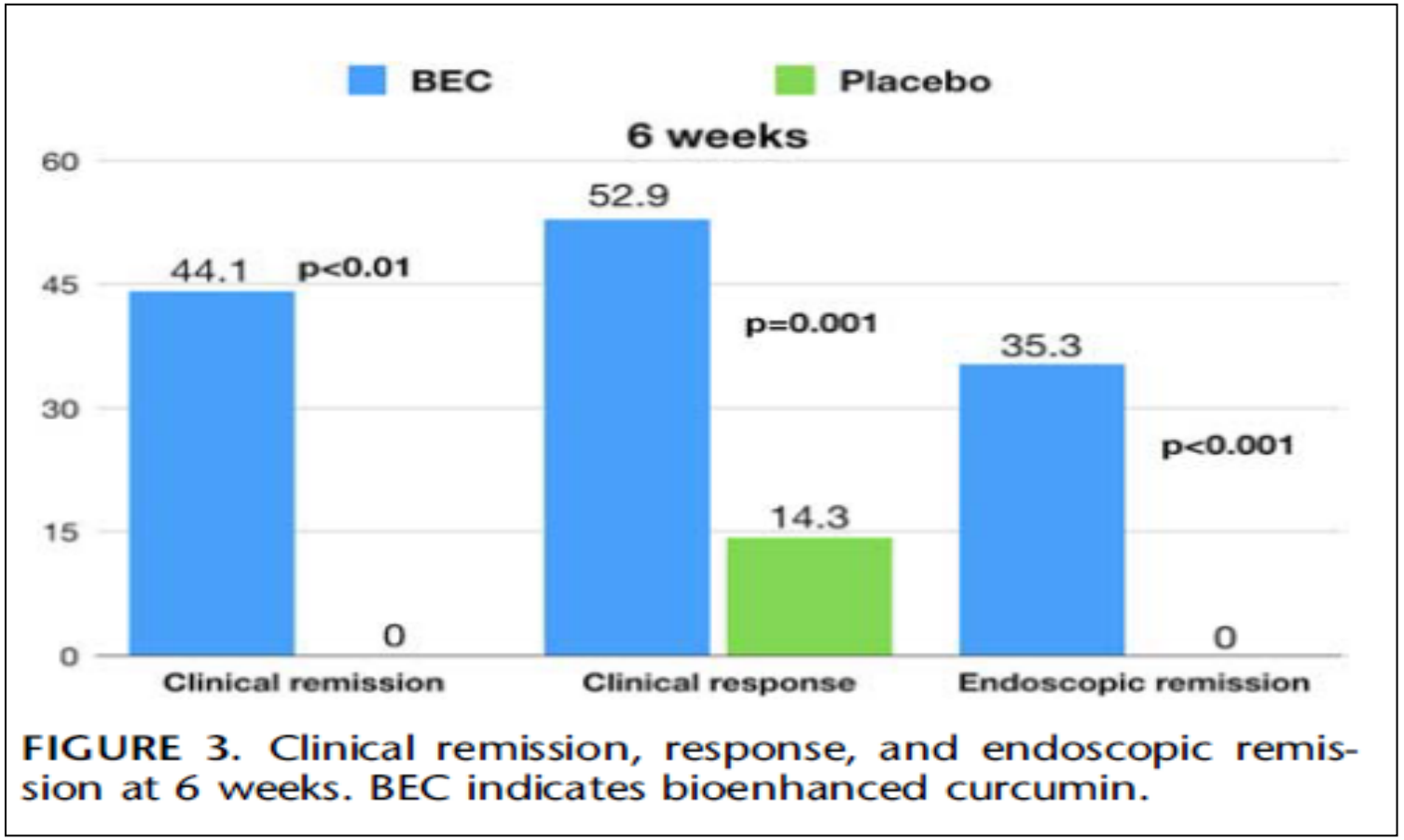
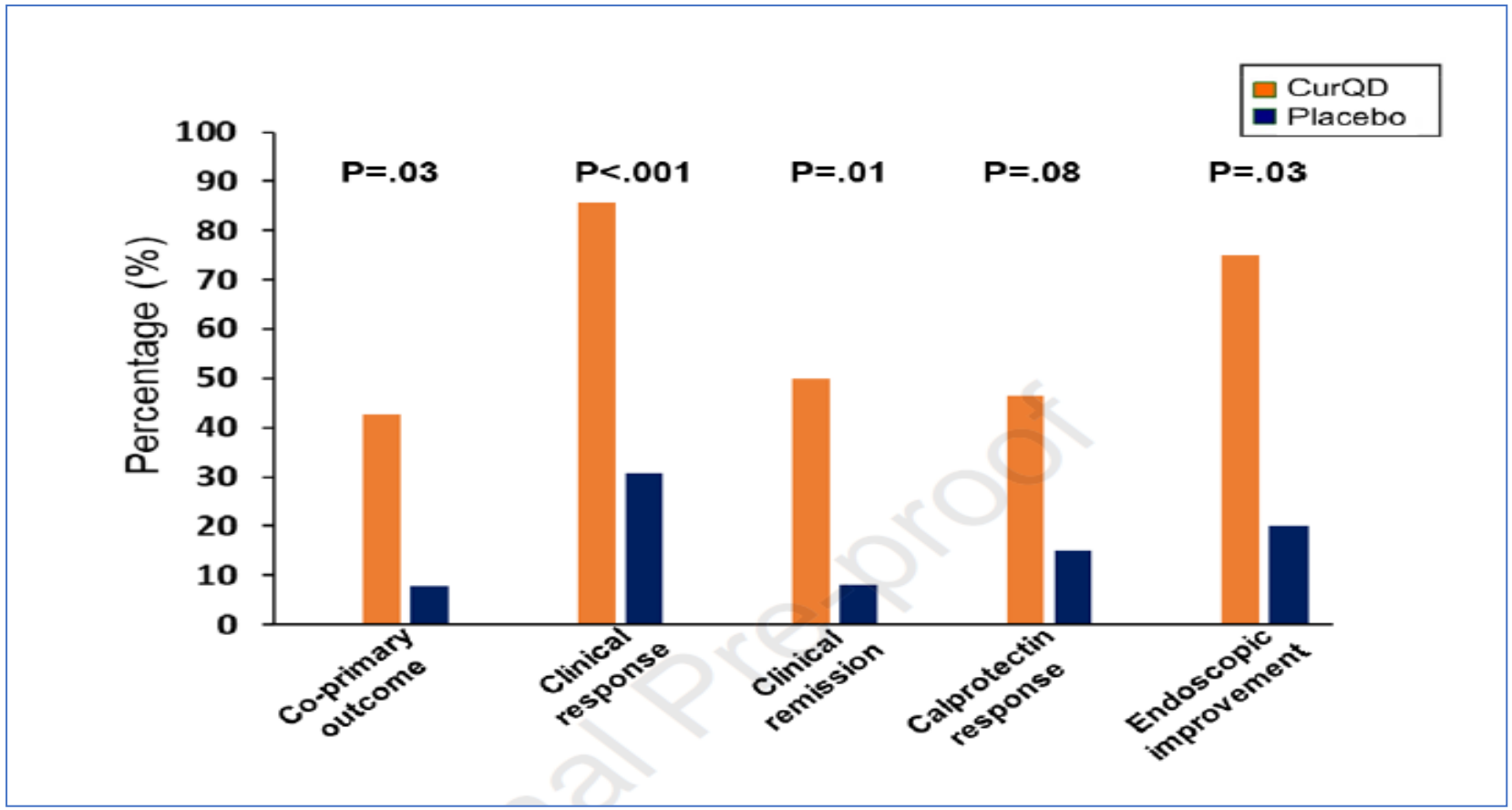


FIGURE 3. Clinical remission, response, and endoscopic remission at 6 weeks. BEC indicates bioenhanced curcumin.

Bioenhanced form of curcumin 100 mg/die

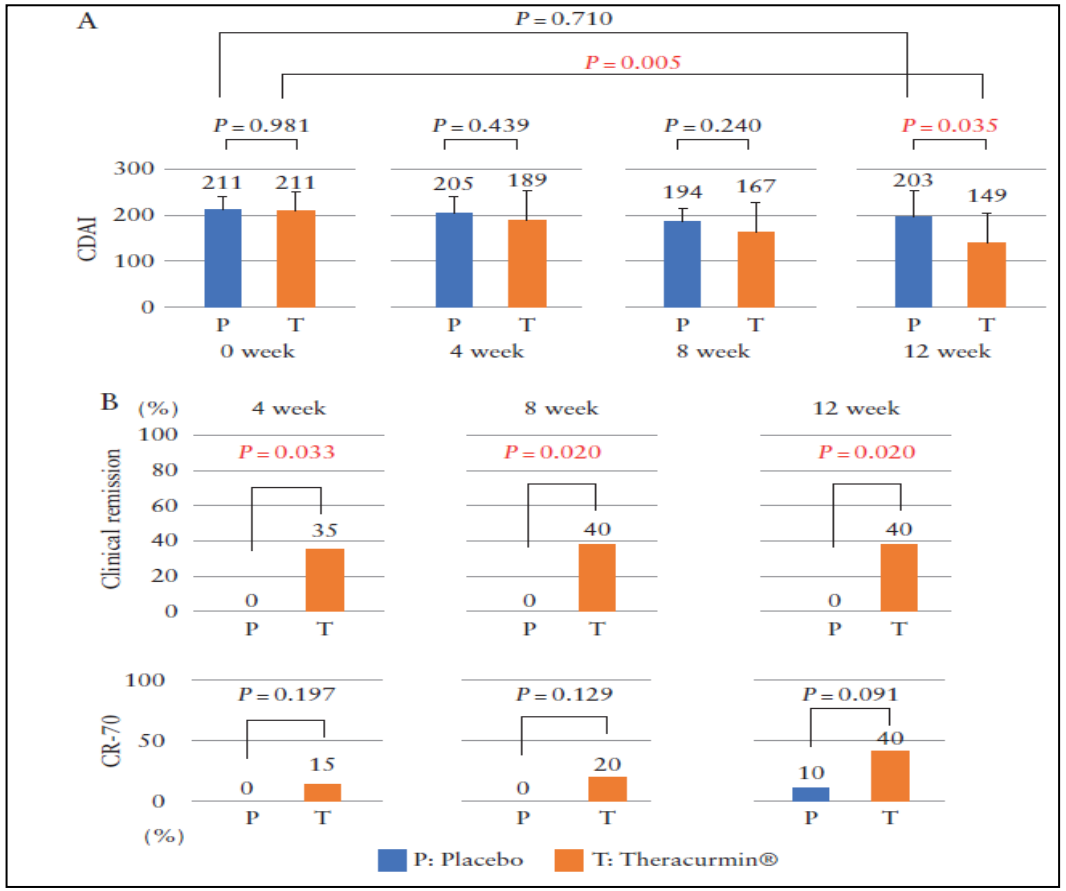
Banerjee et al J Clin Gastroenterol 2021

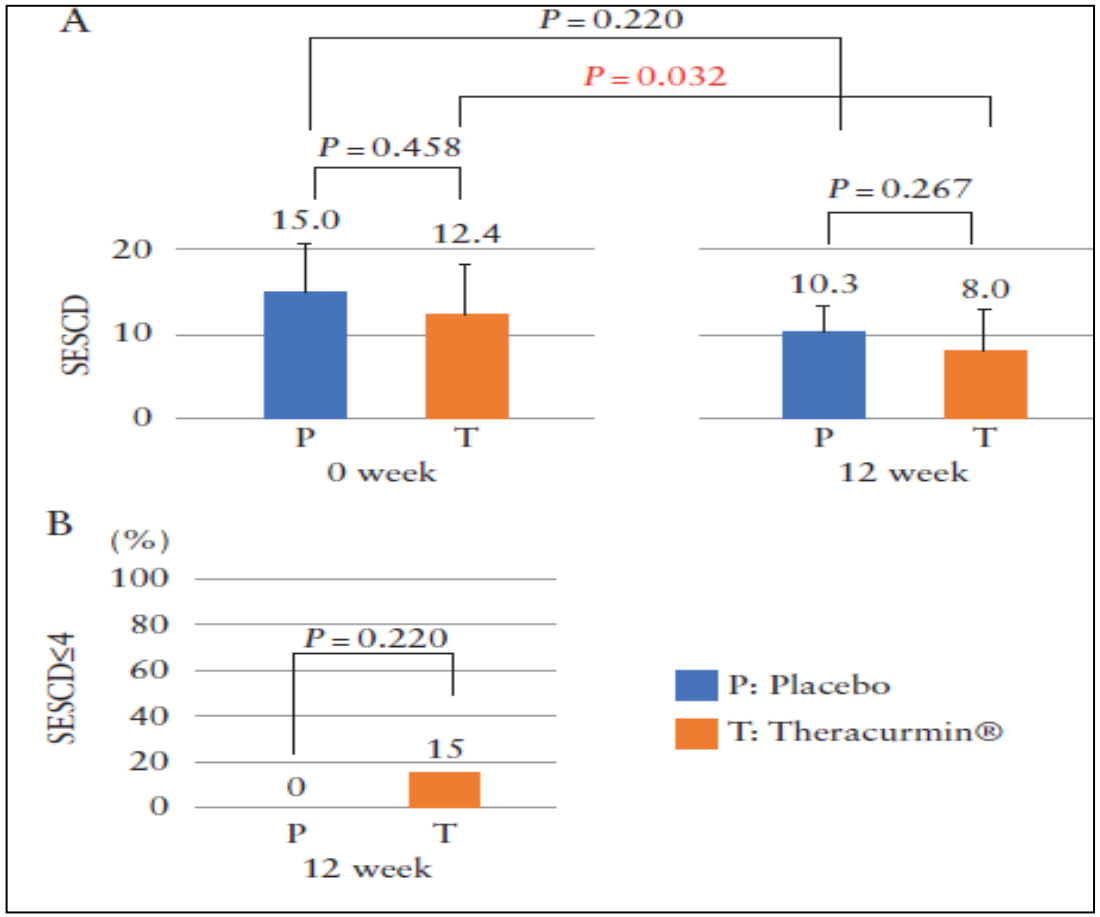
Curcumin-QingDai combination for patients with active ulcerative colitis: A randomized double-blinded placebo-controlled trial



Ben-Horin al, Clin Gastroenterol Hepatol 2023

Highly Bioavailable Curcumin Derivative Ameliorates Crohn's Disease Symptoms: A Randomized, Double-Blind, Multicenter Study

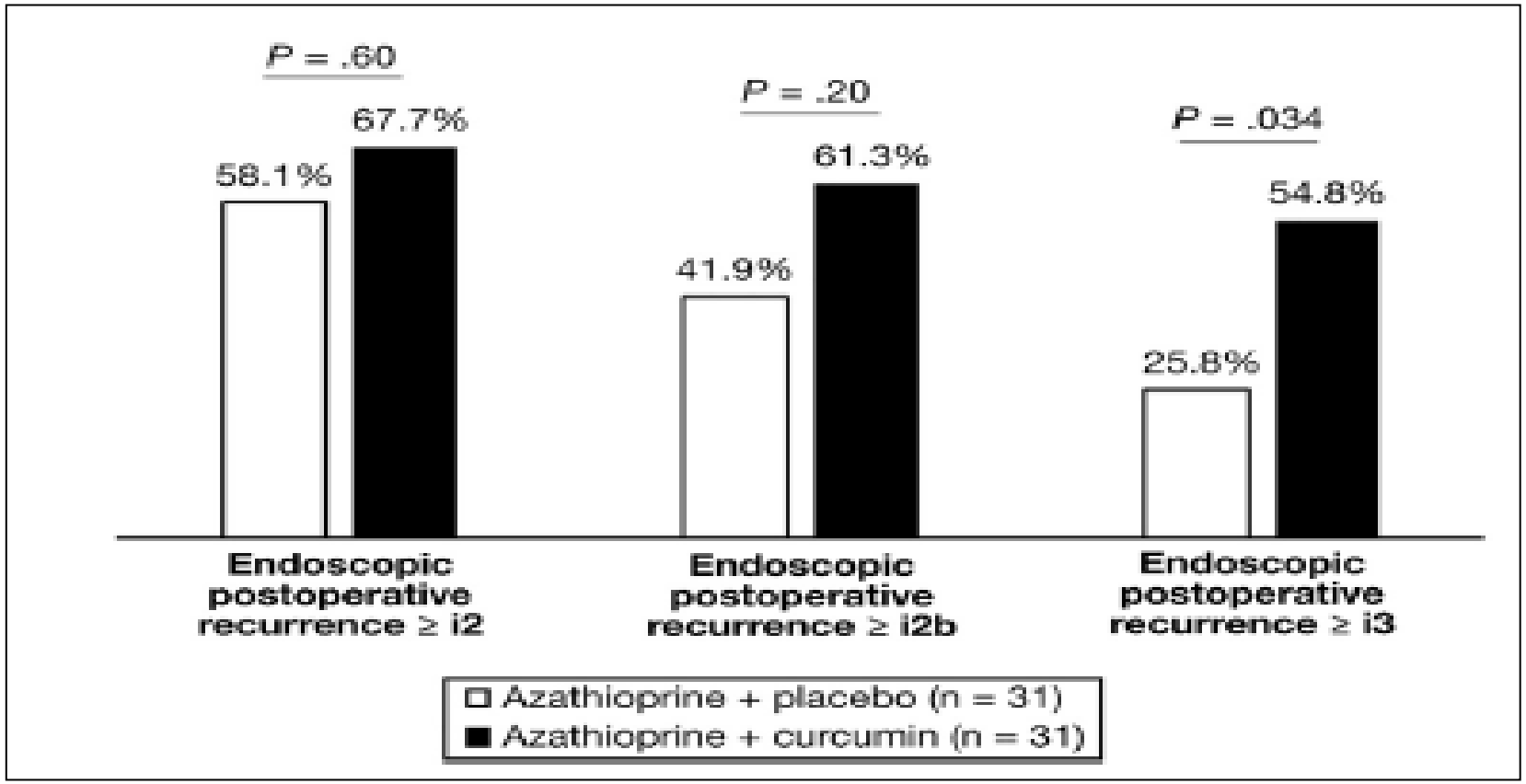




Theracurmin 360 mg/die

Sugimoto et al JCC 2020

Oral Curcumin No More Effective Than Placebo in Preventing Recurrence of Crohn's Disease After Surgery in a Randomized Controlled Trial



Curcurmina 3 gr/die

Bommelaer al, Clin Gastroenterol Hepatol 2020

AGA Technical Review on the Management of Mild-to-Moderate Ulcerative Colitis

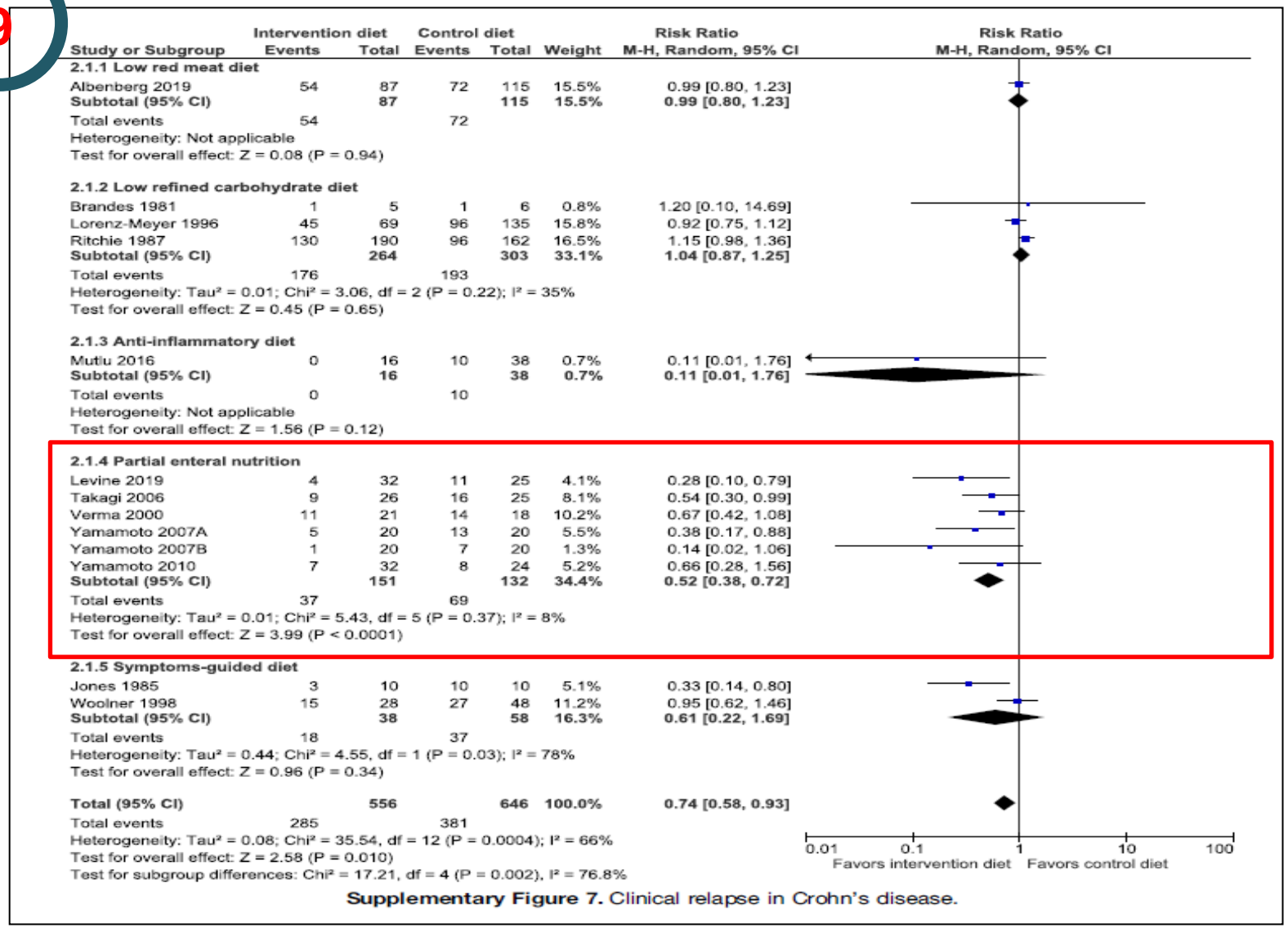
In patients with mild–moderate UC, the benefit of probiotics over placebo, or over mesalamine for induction and maintenance of remission is uncertain (low to very low-quality evidence)

In patients with mild–moderate UC despite 5-ASA therapy, the benefit of adding oral curcumin for induction of remission is unclear (very low-quality evidence), but it may be beneficial for maintenance of remission (low-quality evidence).

Singh et al Gastroenterology 2019

Diete di esclusione nel trattamento delle IBD

- *high fiber*
- *low refined carbohydrates*
- *low microparticle*
- *low calcium*
- *symptoms-guided diet*
- *highly restricted organic diet*
- *low red processed meat diets*
- *Alberta-based anti-inflammatory diet*
- *carrageenan-free diet*
- *milk-free diet*
- *Mediterranean diet*



Supplementary Figure 7. Clinical relapse in Crohn's disease.

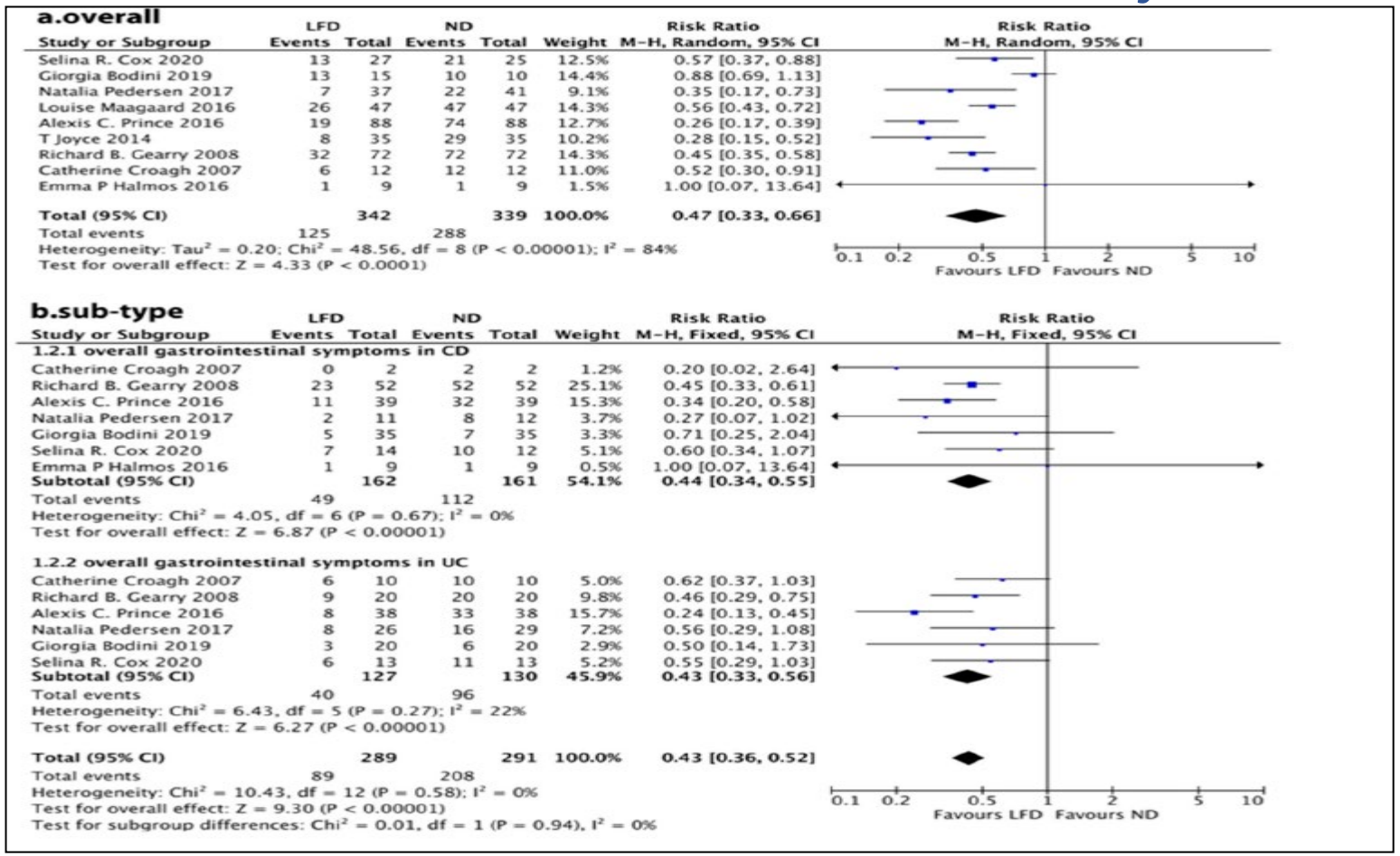
Dietary Interventions for the Treatment of Inflammatory Bowel Diseases: An Updated Systematic Review and Metaanalysis

Among the most robust dietary trials in IBD currently available, ***certainty of evidence remains very low or low.*** *Nonetheless,* ***emerging data suggest potential benefit with PEN for induction and maintenance of remission in CD.*** *Reduction of red meat and refined carbohydrates might not reduce risk of CD relapse. As more dietary studies become available, the certainty of evidence could improve, thus allowing for more meaningful recommendations for patients.*

Limketkai et al CGH 2022

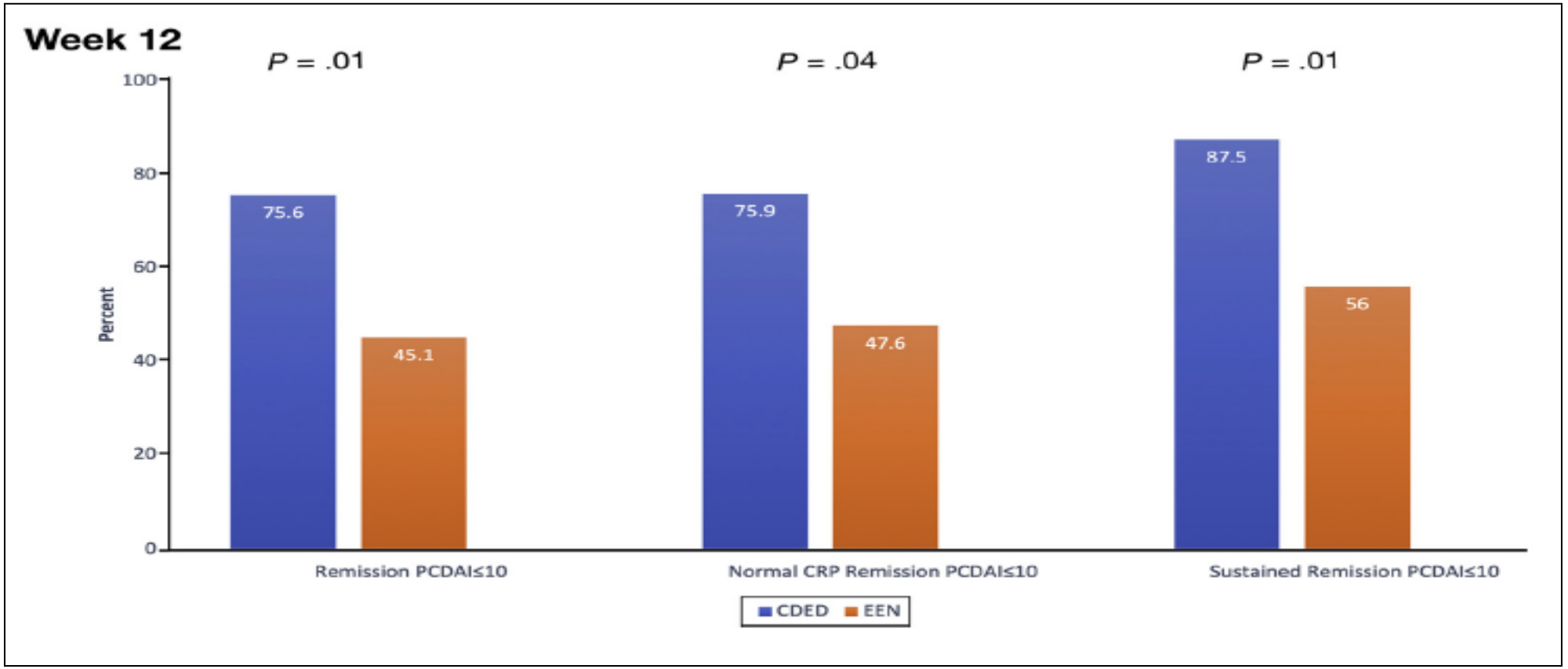
10

A Low-FODMAP Diet Provides Benefits for Functional Gastrointestinal Symptoms but Not for Improving Stool Consistency and Mucosal Inflammation in IBD: A Systematic Review and Meta-Analysis



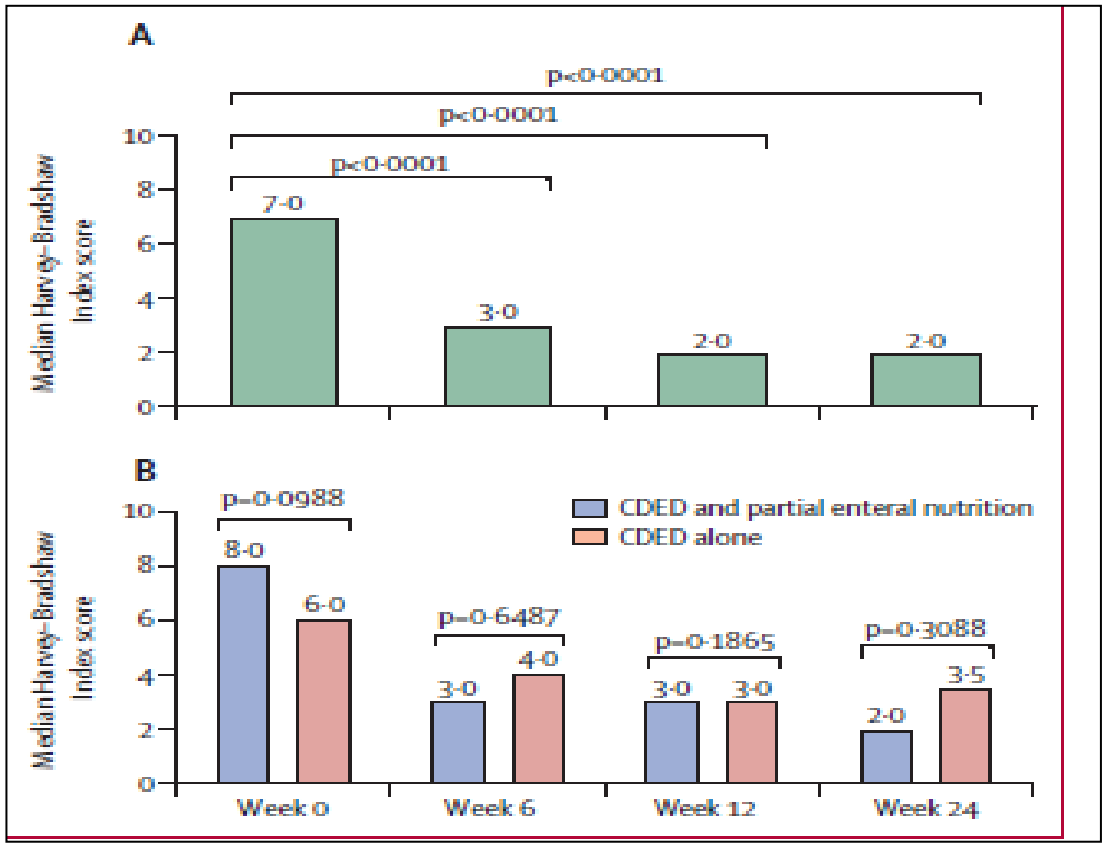
Peng et al Nutrients 2022

Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial



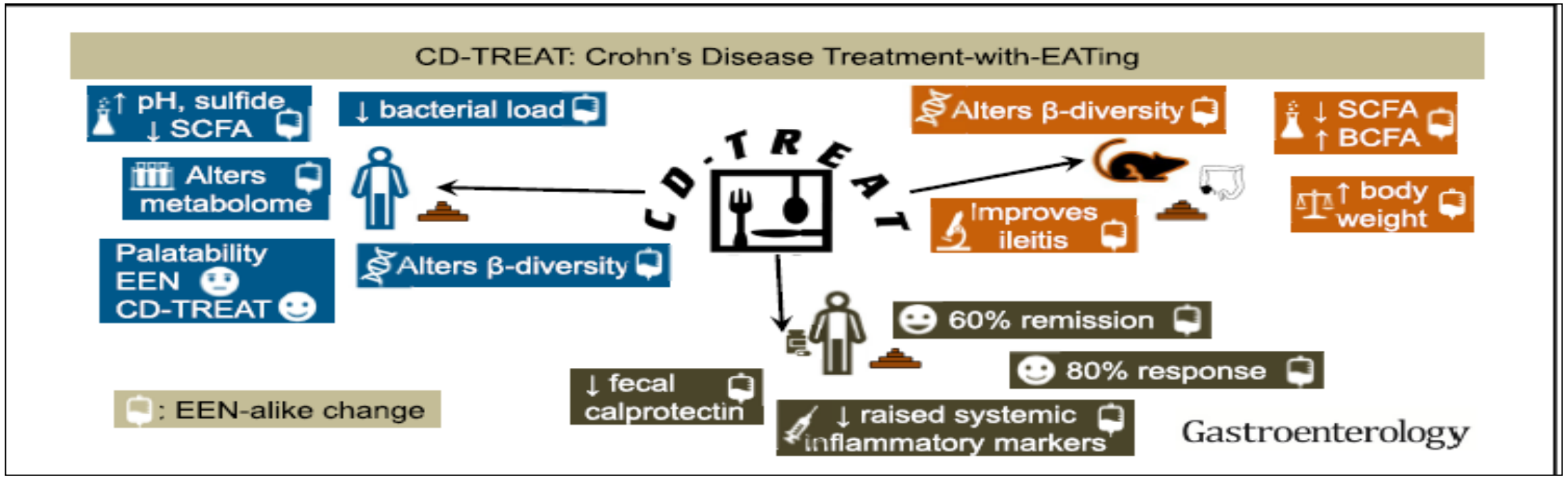
Levine et al Gastroenterol oly 2019

The Crohn's disease exclusion diet for induction and maintenance of remission in adults with mild-to-moderate Crohn's disease (CDED-AD): an open-label, pilot, randomised trial



Yanai et al Lancet Gastroenterol Hepatol 2022

Treatment of Active Crohn's Disease With an Ordinary Food-based Diet That Replicates Exclusive Enteral Nutrition



Svolos et al Gastroenterology 2019

Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels

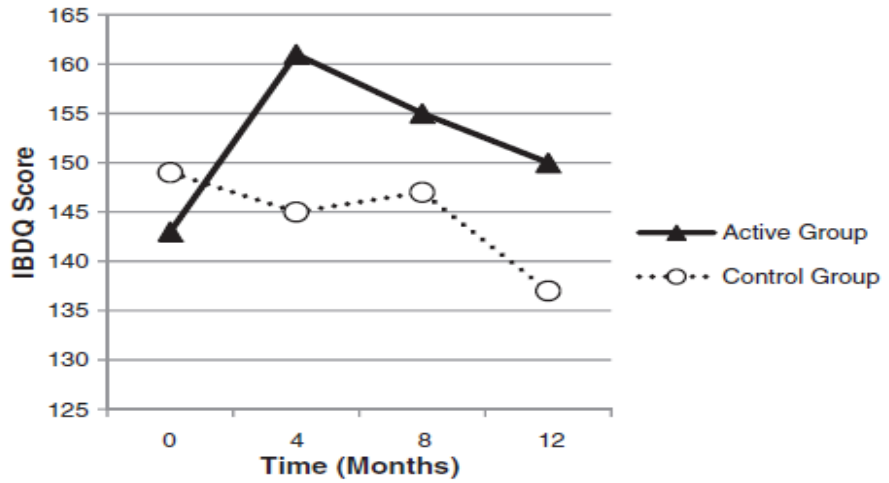


Figure 3 Sub-group analysis for patients with IBS-type symptoms at baseline: progression of IBDQ score during the follow-up period.

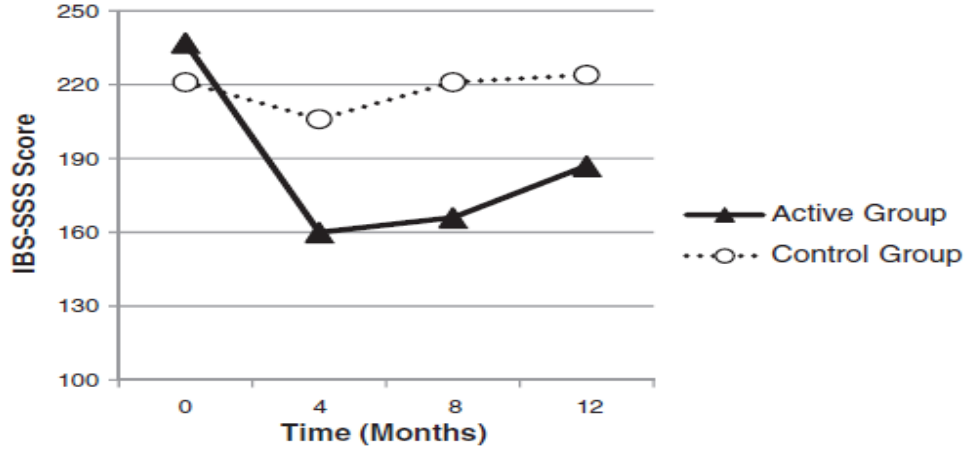
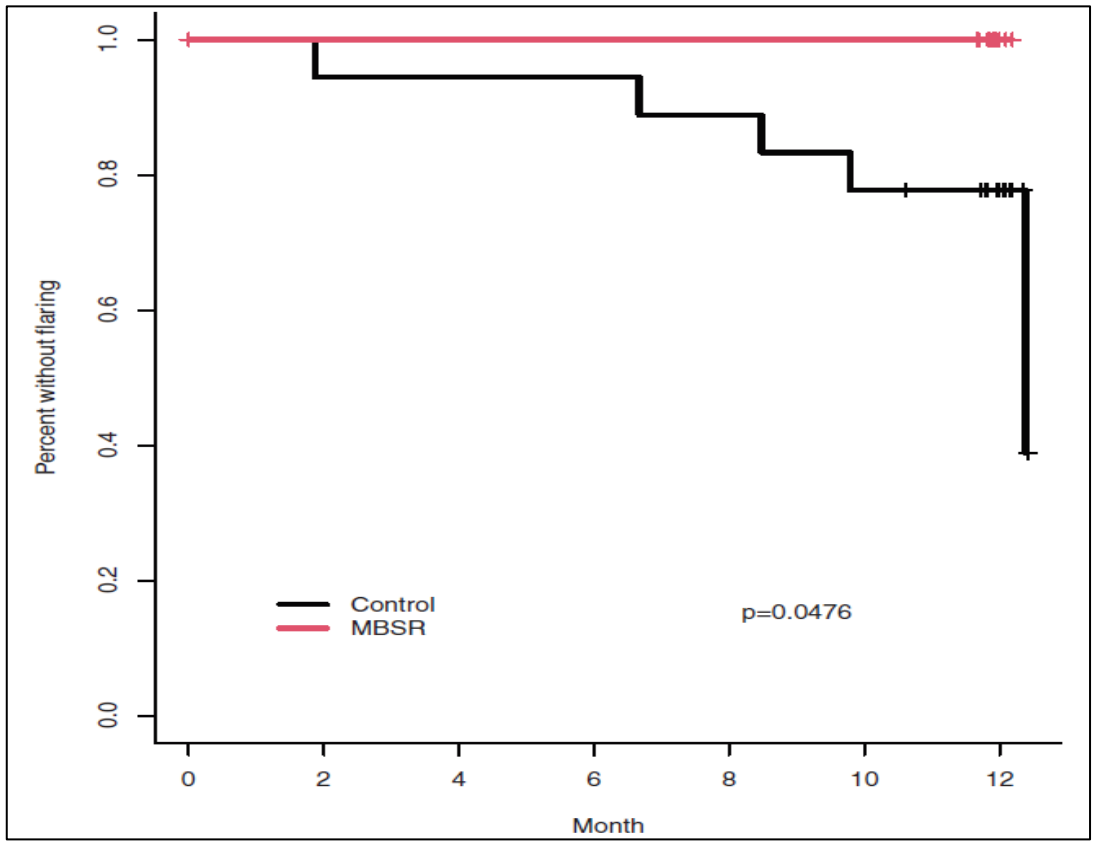


Figure 4 Sub-group analysis for patients with IBS-type symptoms at baseline: severity of IBS symptoms in active and control groups during the follow-up period.

Berrill et al JCC 2014

Mindfulness Intervention Decreases Frequency and Severity of Flares in Inactive Ulcerative Colitis Patients:Results of a Phase II, Randomized, Placebo-Controlled Trial



Jedel et al IBD 2022

Randomised clinical trial: yoga vs written self-care advice for ulcerative colitis

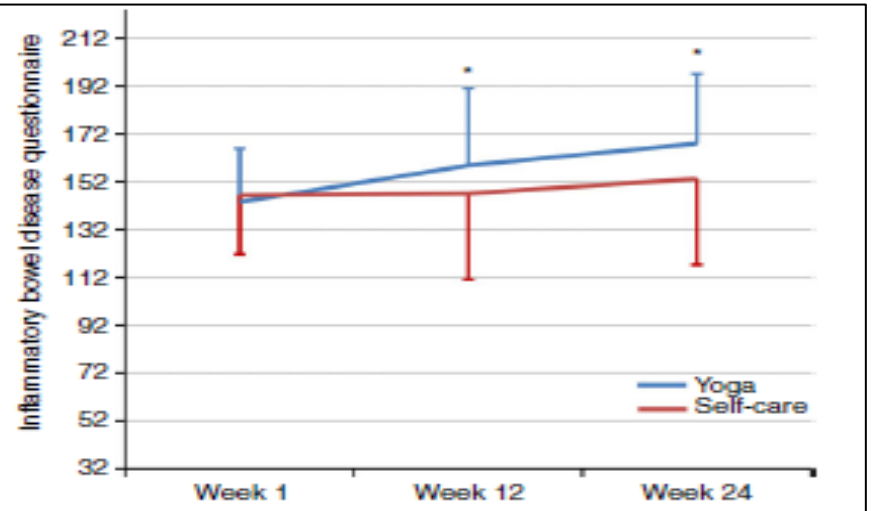


Figure 3 | Effects of yoga and self-care on the primary outcome measure disease-specific quality of life assessed using the Inflammatory Bowel Disease Questionnaire at weeks 1, 12 and 24. Values are expressed as mean ± s.d.; asterisks indicate significant group differences.

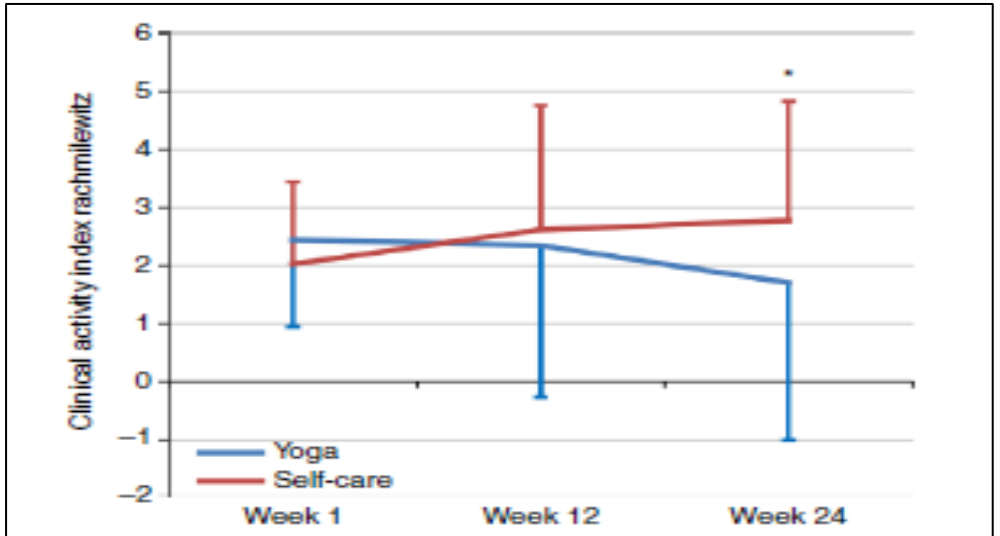


Figure 5 | Effects of yoga and self-care on the Clinical Activity Index according to Rachmilewitz at weeks 1, 12 and 24. Values are expressed as mean ± s.d.; asterisks indicate significant group differences.

Cramer et al APT 2017

Gut-directed hypnotherapy significantly augments clinical remission in quiescent ulcerative colitis

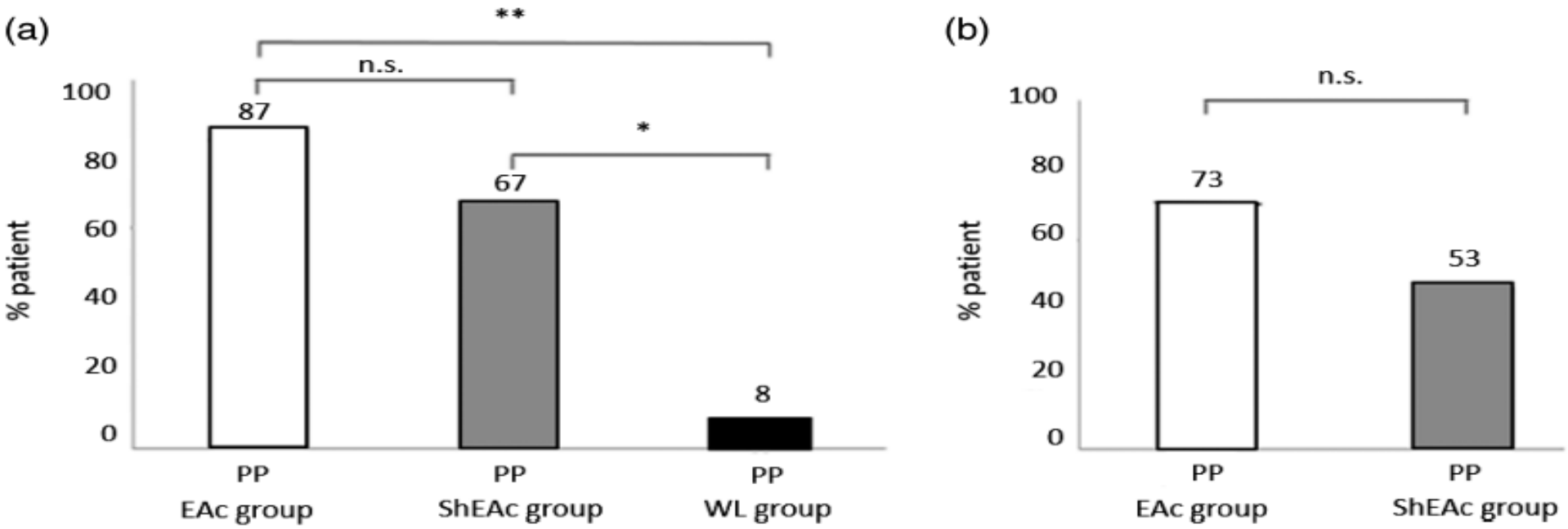
Table 2

Changes in primary outcome measures at 1 year.

Variable	Hypnotherapy (N = 25) Mean (SD)	Attention Control (N = 25) Mean (SD)	Test Statistic
Days to relapse	359.4 (145.9)	281.8 (100.5)	t = 2.1 (1, 48), p = .03
Proportion still in remission at 1 year	17 (68%)	10 (40%)	X^2 (1) = 3.9, p = .04
IBDQ	↑2.3 (24.1)	↓7.9 (20.7)	t (1,48) = .24, p = ns

Keefer et al APT 2013

A Prospective Pilot Randomized Study: Electroacupuncture vs. Sham Procedure for the Treatment of Fatigue in Patients With Quiescent Inflammatory Bowel Disease



*p<0.01; ** p< 0.001; n.s, non-significant
PP, per-protocol analysis; EAc, electroacupuncture; ShEAc, sham electroacupuncture; WL, wait-list

Horta et al IBD 2020

1

Probiotici nella terapia delle malattie infiammatorie intestinali

top ten in gastroenterologia
14^ EDIZIONE
24-25 NOVEMBRE 2023
BERGAMO

- *Formulazione De Simone*
- *Escherichia coli Nissle 1917*
- *Saccharomyces boulardii*
- *Lactobacillus (GG, acidophilus, rhamnosus, plantarum, reuteri)*
- *Bifidobacterium (longum, breve)*
- *Enterococcus spp*

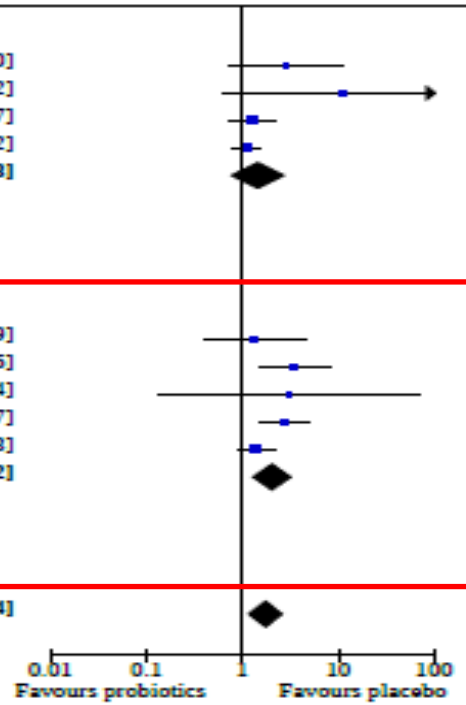
2

Probiotics for induction of remission in ulcerative colitis

top ten in gastroenterologia
14^ EDIZIONE
24-25 NOVEMBRE 2023
BERGAMO

Analysis 1.3. Comparison 1: Probiotics versus placebo, Outcome 3: Clinical remission: subgroup analysis by number of strains

Study or Subgroup	Probiotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Single strain						
Matthes 2010	20	70	2	20	6.0%	2.86 [0.73 , 11.20]
Oliva 2011	5	20	0	20	1.7%	11.00 [0.65 , 186.62]
Tamaki 2016	15	28	12	28	16.7%	1.25 [0.72 , 2.17]
Vejdani 2017	14	17	13	17	21.1%	1.08 [0.76 , 1.52]
Subtotal (95% CI)		**135**		**85**	**45.4%**	**1.44 [0.79 , 2.63]**
Total events:	54		27			
Heterogeneity: Tau² = 0.18; Chi² = 7.00, df = 3 (P = 0.07); I² = 57%						
Test for overall effect: Z = 1.18 (P = 0.24)						
1.3.2 Multiple strains						
Kato 2004	4	10	3	10	7.1%	1.33 [0.40 , 4.49]
Miele 2009	13	14	4	15	11.2%	3.48 [1.49 , 8.16]
Sanchez-Morales 2019	1	17	0	17	1.4%	3.00 [0.13 , 68.84]
Sood 2009	33	77	11	70	15.6%	2.73 [1.50 , 4.97]
Tursi 2010	31	71	23	73	19.3%	1.39 [0.90 , 2.13]
Subtotal (95% CI)		**189**		**185**	**54.6%**	**2.02 [1.31 , 3.12]**
Total events:	82		41			
Heterogeneity: Tau² = 0.08; Chi² = 5.89, df = 4 (P = 0.21); I² = 32%						
Test for overall effect: Z = 3.18 (P = 0.001)						
Total (95% CI)		**324**		**270**	**100.0%**	**1.73 [1.19 , 2.54]**
Total events:	136		68			
Heterogeneity: Tau² = 0.15; Chi² = 17.89, df = 8 (P = 0.02); I² = 55%						
Test for overall effect: Z = 2.84 (P = 0.005)						
Test for subgroup differences: Chi² = 0.80, df = 1 (P = 0.37), I² = 0%						



Kaur et al Cochrane Library 2020

3

Probiotics for induction of remission in ulcerative colitis

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Low-certainty evidence *suggests that probiotics* ***may induce clinical remission in active ulcerative colitis when compared to placebo.***

There may be little or no difference in clinical remission with probiotics alone compared to 5-ASA.

There is limited evidence from a single study *which failed to provide a definition of remission, that probiotics* ***may slightly improve the induction of remission when used in combination with 5-ASA.***

There was no evidence to assess whether probiotics are effective in people with severe and more extensive disease, or if specific preparations are superior to others.

Further targeted and appropriately designed RCTs are needed to address the gaps in the evidence base*. In particular, appropriate powering of studies and the use of standardised participant groups and outcome measures in line with the wider field are needed, as well as reporting to minimise risk of bias.*

Kaur et al Cochrane Library 2020

4

Escherichia coli Nissle 1917 vs mesalazina nella colite ulcerosa in remissione: metaanalisi

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Study or Subgroup	EcN Events	EcN Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Henker 2008	8	24	3	10	6.8%	1.17 [0.24, 5.76]
Kruis 1997	8	50	6	53	11.7%	1.49 [0.48, 4.65]
Kruis 2004	40	110	38	112	57.5%	1.11 [0.64, 1.93]
Rembacken 1999	26	39	32	44	24.0%	0.75 [0.29, 1.92]
Total (95% CI)		**223**		**219**	**100.0%**	**1.07 [0.70, 1.64]**
Total events	82		79			

Heterogeneity: Chi² = 0.91, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

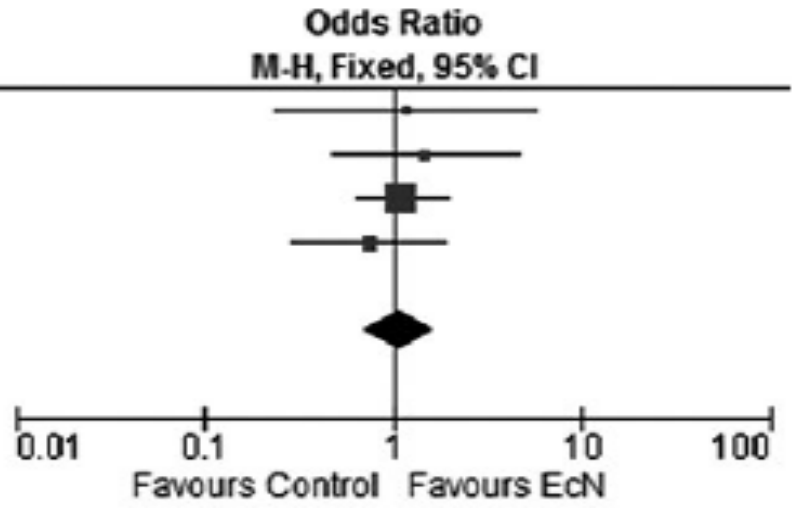

Fig. 3. Forest plot of the efficacy of EcN in maintaining remission for ulcerative colitis.

Losurdo et al J Gastrointestin Liver Dis 2015

5

Probiotics for maintenance of remission in ulcerative colitis

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***The effectiveness of probiotics for the maintenance of remission in ulcerative colitis remains unclear**.*
***This is due to low- to very low certainty evidence from poorly conducted studies**, which contribute limited amounts of data from a small number of participants.*
***Future trials comparing probiotics with 5-ASA rather than placebo will better reflect conventional care** given to people with ulcerative colitis. Appropriately powered studies with a minimum length of 12 months are needed*

Iheozor-Ejiofor et al Cochrane Library 2020

6 Treatment and prevention of pouchitis aer ileal pouch-anal anastomosis for chronic ulcerative colitis

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*For chronic pouchitis, **low quality evidence** suggests that VSL#3 may be more effective than placebo for maintenance of remission.*

*For the prevention of pouchitis, **low quality evidence** suggests that VSL#3 may be more eLective than placebo.*

***Well designed, adequately powered studies are needed** to determine the optimal therapy for the treatment and prevention of pouchitis*

Singh et al Cochrane Library 2015

Probiotici nella terapia della colite ulcerosa
Possibili indicazioni

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- *Formulazione de Simone nella terapia di mantenimento della pouchite antibiotico-dipendente*
- *E.Coli Nissle 1917 nella terapia di mantenimento della colite ulcerosa* ***in pazienti intolleranti a mesalazina***
- *Probiotici contenenti ceppi* ***multipli in aggiunta a mesalazina*** *nella terapia di mantenimento della colite ulcerosa*

Novel Bioenhanced Curcumin With Mesalamine for Induction of Clinical and Endoscopic Remission in Mild-to-Moderate Ulcerative Colitis

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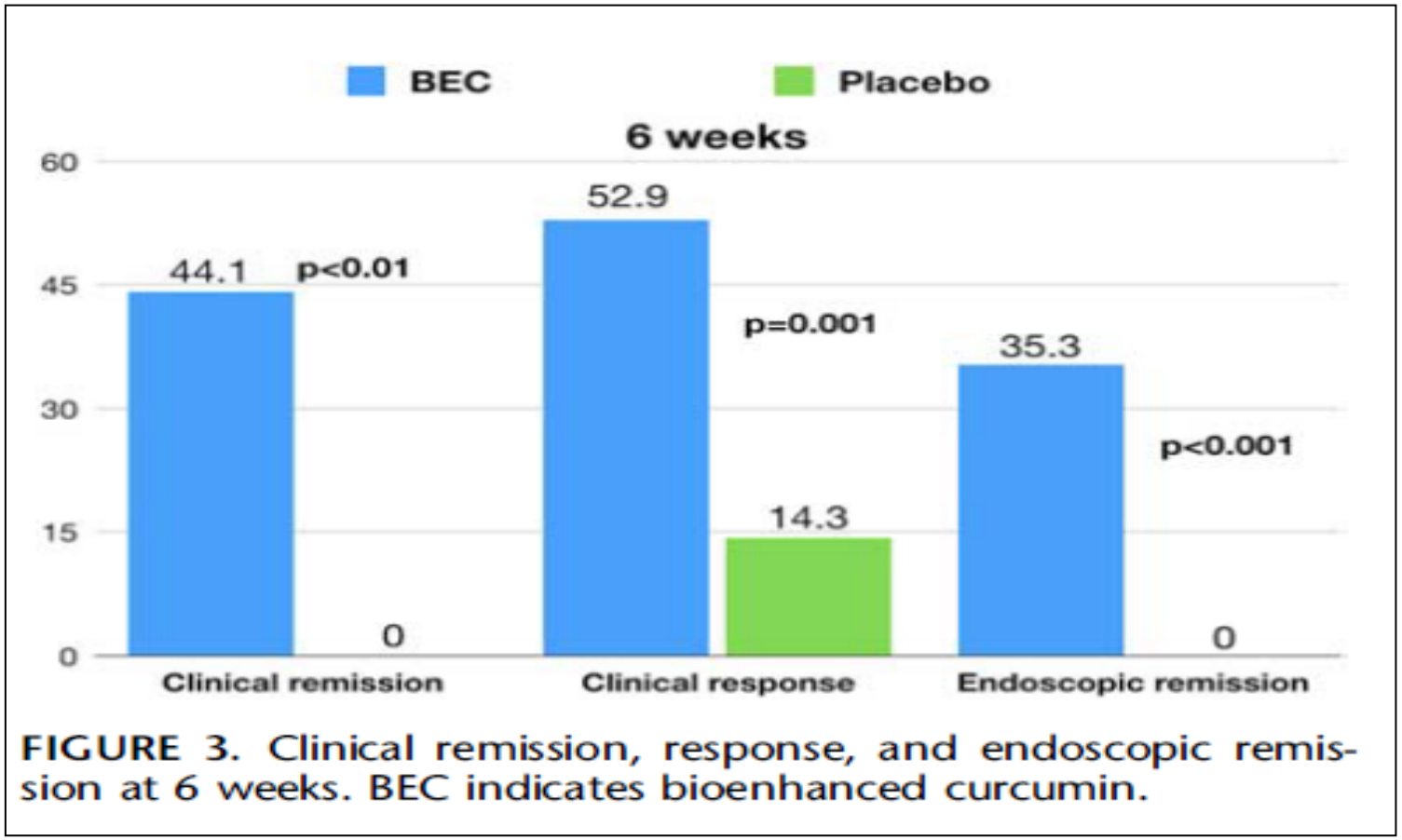

FIGURE 3. Clinical remission, response, and endoscopic remission at 6 weeks. BEC indicates bioenhanced curcumin.

Banerjee et al J Clin Gastroenterol 2021

Dietary Interventions for the Treatment of Inflammatory Bowel Diseases: An Updated Systematic Review and Metaanalysis

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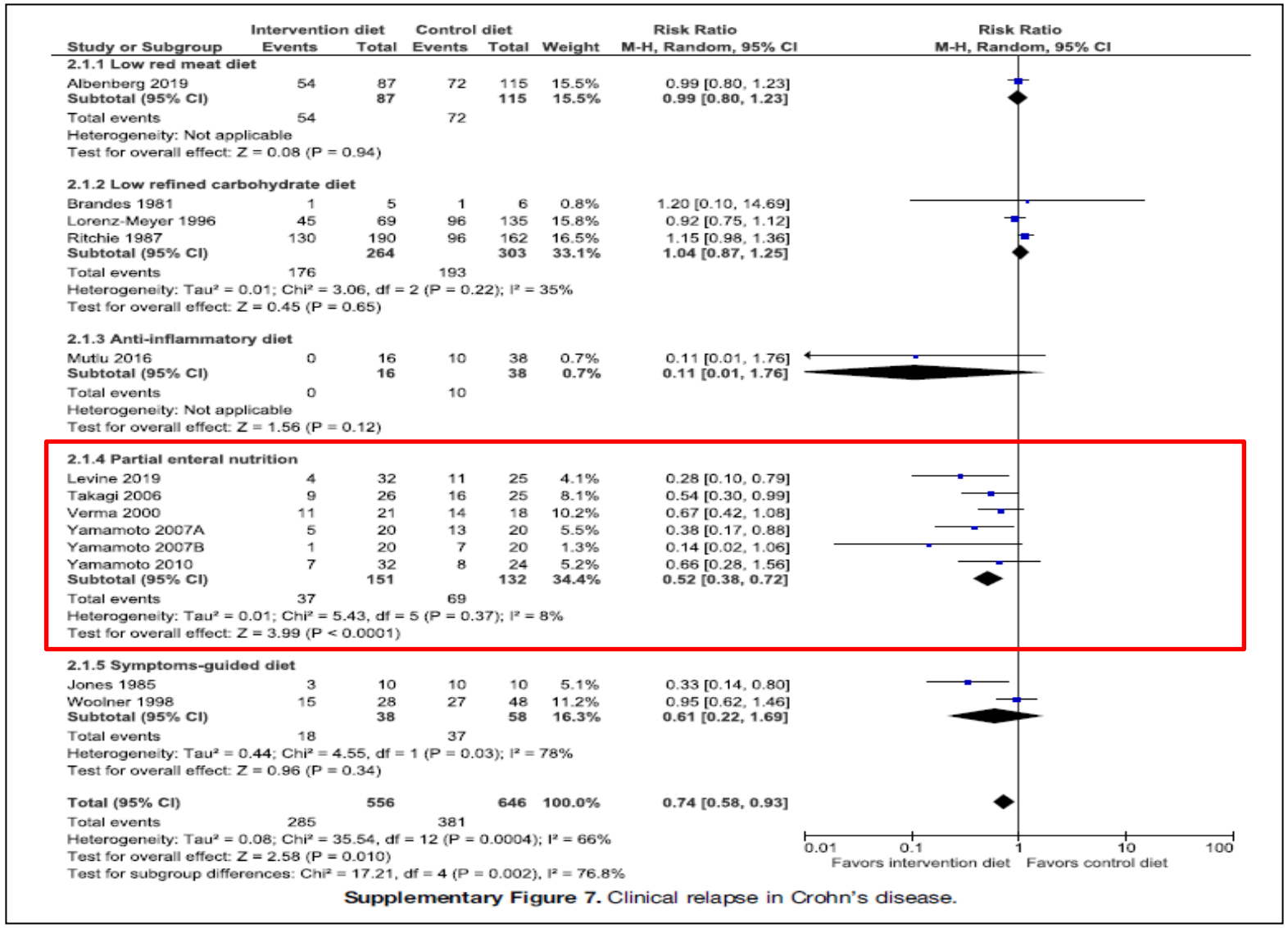

Supplementary Figure 7. Clinical relapse in Crohn's disease.

Among the most robust dietary trials in IBD currently available, ***certainty of evidence remains very low or low.*** *Nonetheless,* ***emerging data suggest potential benefit with PEN for induction and maintenance of remission in CD.*** *Reduction of red meat and refined carbohydrates might not reduce risk of CD relapse. As more dietary studies become available, the certainty of evidence could improve, thus allowing for more meaningful recommendations for patients.*

Limketkai et al CGH 2022

10

A Low-FODMAP Diet Provides Benefits for Functional Gastrointestinal Symptoms but Not for Improving Stool Consistency and Mucosal Inflammation in IBD: A Systematic Review and Meta-Analysis

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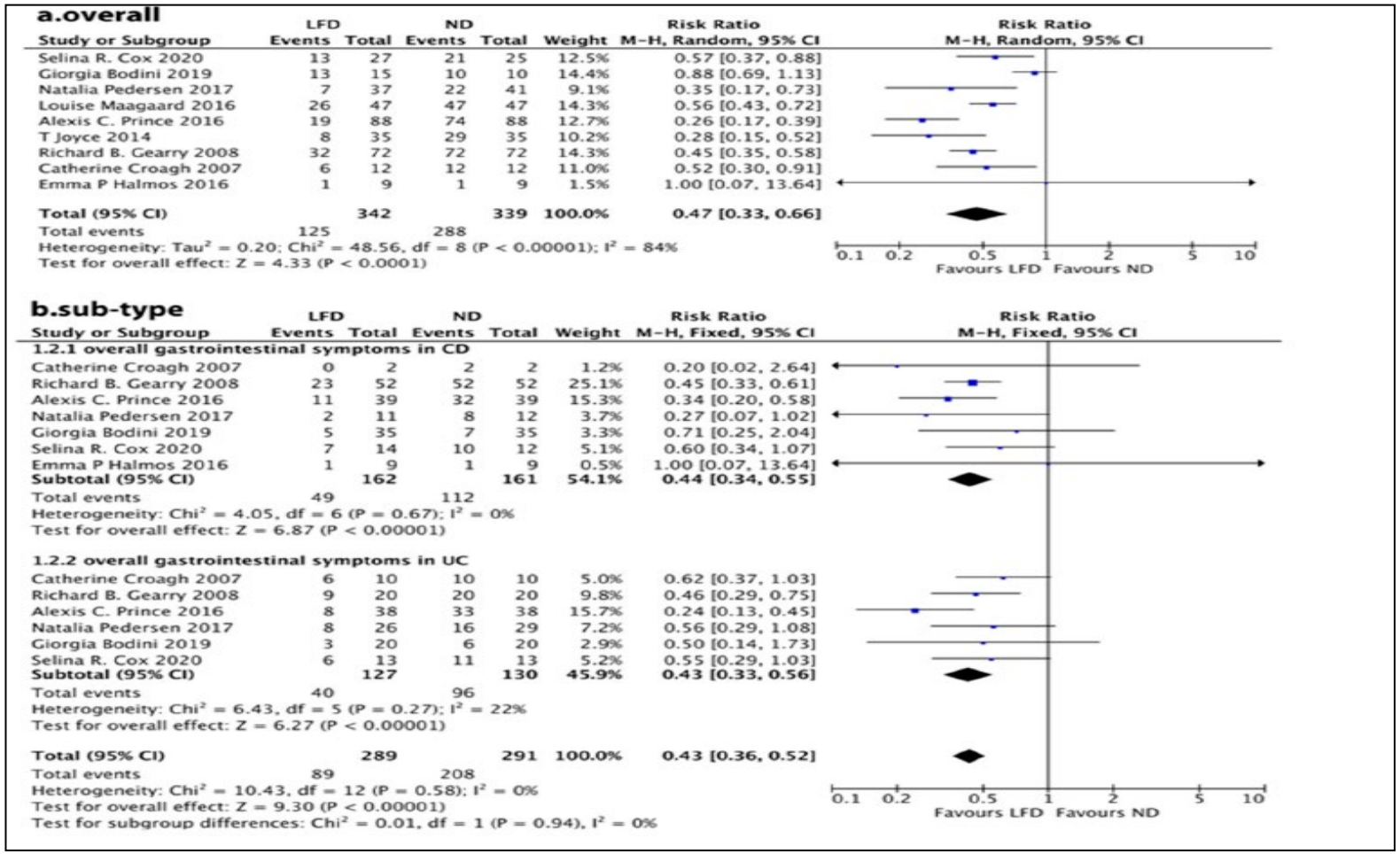

Peng et al Nutrients 2022